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# E-Cigarettes and Cardiopulmonary Health: Review for Clinicians

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**ABSTRACT:** Electronic cigarettes (e-cigarettes) are battery powered electronic nicotine delivery systems that use a propylene glycol/vegetable glycerin base to deliver vaporized nicotine and flavorings to the body. E-cigarettes became commercially available without evidence regarding their risks, long-term safety, or utility in smoking cessation. Recent clinical trials suggest that e-cigarette use with counseling may be effective in reducing cigarette use but not nicotine dependence. However, meta-analyses of observational studies demonstrate that e-cigarette use is not associated with smoking cessation. Cardiovascular studies reported sympathetic activation, vascular stiffening, and endothelial dysfunction, which are associated with adverse cardiovascular events. The majority of pulmonary clinical trials in e-cigarette users included standard spirometry as the primary outcome measure, reporting no change in lung function. However, studies reported increased biomarkers of pulmonary disease in e-cigarette users. These studies were conducted in adults, but >30% of high school–age adolescents reported e-cigarette use. The effects of e-cigarette use on cardiopulmonary endpoints in adolescents and young adults remain unstudied. Because of adverse clinical findings and associations between e-cigarette use and increased incidence of respiratory diseases in people who have never smoked, large longitudinal studies are needed to understand the risk profile of e-cigarettes. Consistent with the Centers for Disease Control and Prevention recommendations, clinicians should monitor the health risks of e-cigarette use, discourage nonsmokers and adolescents from using e-cigarettes, and discourage smokers from engaging in dual use without cigarette reduction or cessation.

**Key Words:** cardiovascular system ■ electronic nicotine delivery systems ■ lung injury ■ nicotine ■ smoking



Electronic cigarettes (e-cigarettes) are a relatively new and developing electronic nicotine delivery system that became commercially available in 2004. The long-term cardiopulmonary effects of e-cigarettes remain poorly understood. Maintaining up-to-date knowledge on e-cigarettes is a challenge for clinicians, especially because e-cigarettes continue to change in engineering design and chemical composition and are often released commercially without clinical safety or smoking cessation efficacy data. E-cigarettes are battery-powered heating elements connected to a tank or reservoir that contains a mixture of nicotine, flavors, and other chemicals dissolved in a propylene glycol/vegetable glycerin vehicle of varying ratios (Figure 1).[1]

The first 2 generations of e-cigarettes were inefficient at increasing plasma nicotine compared with combustible tobacco products. In contrast, high-powered third-generation devices achieved similar plasma nicotine levels and pharmacokinetics as tobacco cigarettes.[2] Fourth-generation e-cigarette devices (eg, JUUL, Puff Bar) switched from freebase nicotine to nicotine salt and benzoic acid.[3] Previous research has indicated that less e-liquid is consumed when using devices with higher nicotine content.[2] Therefore, more efficient nicotine delivery could reduce overall exposure to e-cigarette aerosol; however, this has not been directly studied in fourth-generation devices relative to older models. Fourth-generation e-cigarette devices are readily available in both rechargeable and

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## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **EVALI** | e-cigarette or vaping product use–associated lung injury |
| **NRT** | nicotine replacement therapy |
| **OR** | odds ratio |
| **PWV** | pulse wave velocity |
| **THC** | tetrahydrocannabinol |

disposable forms with limited regulation. The effect of e-cigarettes on cardiopulmonary health only beginning to be understood.

## UNRESOLVED ISSUES

It has been suggested that e-cigarettes improve smoking cessation rates (which has been contested and is discussed in detail later in this review). Therefore, if e-cigarettes are to be used as a transition to stop tobacco cigarette use, understanding the relative harms of e-cigarette use versus tobacco cigarette smoking is vital for clinicians considering e-cigarettes as a potential treatment option for smokers. On the other hand, the absolute harms of e-cigarettes, including their potential to cause nicotine addiction and encourage cigarette smoking, must be considered when discussing health risks with nontobacco cigarette smoking patients.

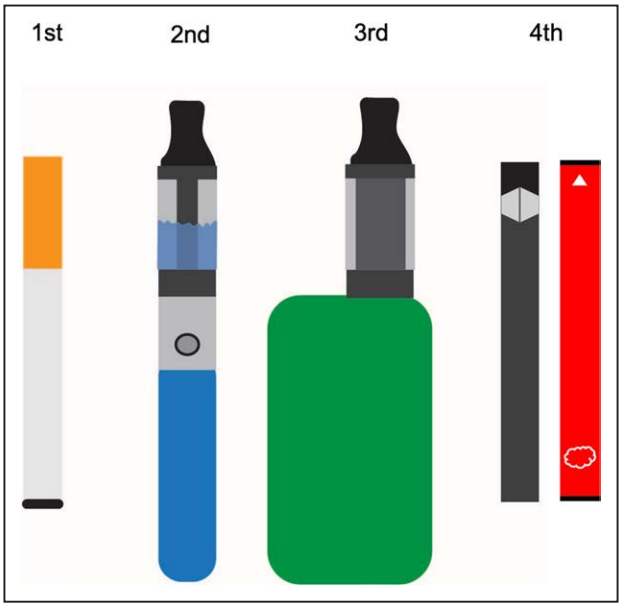


**Figure 1. First- to fourth-generation e-cigarette devices.** From left to right: first-generation ("cig a-likes"), second-generation ("vape pens"), third-generation ("tanks" and "mods"), and fourth-generation ("pod mods") e-cigarette devices. First- and second-generation e-cigarette devices were tubular and inefficient in nicotine delivery when compared with combustible tobacco products. Third-generation devices were customizable and contained larger tanks with larger, higher-voltage batteries and were comparable to conventional cigarettes in nicotine delivery efficiency. Fourth-generation (eg, JUUL, Puff Bar) devices have smaller tanks (pods) and batteries with decreased nicotine delivery efficiency. However, fourth-generation e-cigarettes compensated for lost efficiency by switching from freebase nicotine (used in first-third generation devices) to higher concentrations of nicotine salt, along with benzoic acid. These devices are available in reusable (left) and disposable (right) forms.

The use of e-cigarettes has increased in adolescents[4] (+14.4% from 2017 to 2019, n=4513 [12th graders]) and young adults[5] (+2.5% from 2014 to 2018, n=1857 [age 18–24 years]). In 2019, self-reported past 30-day use of e-cigarettes was 27.5% in adolescents (grades 9–12; n=10 097) and 10.5% in early adolescents (grades 6–8; n=8837).[6] The perception of reduced harm associated with e-cigarette aerosol inhalation (vaping) compared with traditional cigarette smoking has contributed to their uptake by people who have never smoked (never-smokers)[7]; however, smoking cessation is not a primary reason for vaping among youth and young adults.[8] Rather, a meta-analysis of longitudinal studies showed that e-cigarette use in adolescents and young adults is associated with subsequent cigarette smoking initiation (odds ratio [OR] 3.62 [95% CI, 2.42–5.41]).[9] More than $110 million was spent on e-cigarette advertising in 2018,[10] which may have contributed to the increased uptake of e-cigarettes.[11] Youth may be influenced by such promotions and develop a receptive attitude toward product use.[12–14] After a congressional hearing in 2019, the US Food and Drug Administration issued a warning regarding youth-facing advertisement strategies used by JUUL Labs. In 2020, the Food and Drug Administration passed legislation to reduce sales of e-cigarettes to underage users (<18 years old), banning the sale of most fourth-generation flavored cartridge pods.[15] However, this legislation did not apply to disposable e-cigarettes, which became widespread in the following months. The American Heart Association has reported its positions on e-cigarette regulation and long-term goals.[16]

For clinicians, clarity is required regarding the potential clinical utility of e-cigarettes to aid in tobacco cigarette cessation and the potential public health crisis predicated on an increase in youth/young adult nicotine addiction and transition to tobacco cigarette use.[17] As devices continue to evolve and become more palatable, efficient, sleek, and easy to use, smokers may be more likely to transition away from traditional cigarettes. However, these attractive features coincide with youth appeal. Clinicians should balance these perspectives when making individual decisions with their patients and when discussing these devices in health education settings and on media platforms, all of which can affect public opinion and discourse. To assist clinicians in making these decisions, this review examines the epidemiologic data of e-cigarette use, reviews the current state of knowledge on the efficacy of e-cigarettes as a smoking cessation tool, and examines the effects of e-cigarettes on cardiopulmonary health.

## Search Strategy

PubMed and the Cochrane Central Register of Controlled Trials were searched for English-language studies related to e-cigarettes from January 2012 through November 2020. PubMed article type filters were applied to search for controlled clinical trials, randomized controlled trials, meta-analyses, and systematic reviews (see Supplemental search terms). This search resulted in 384 results, which were screened by the authors. Articles were then selected with consideration given to the general medical readership. Reviewing the references of screened articles identified additional observational studies. A select few clinical studies, observational studies, and laboratory studies that were not represented in our searches were incorporated as well (see Supplemental Material). Separate, smaller searches were used to identify epidemiologic studies and studies related to e-cigarette or vaping product use–associated lung injury (EVALI).

## Disease Epidemiology

Epidemiologic studies on vaping, including meta-analyses, have been performed (Table 1). Associations were reported between e-cigarette use and higher incidence of asthma (OR, 1.39–3.41 [95% CI, 1.15–6.49]),[18,19] respiratory disease (OR, 1.31–2.58 [95% CI, 1.03–4.89]),[20–22] COVID-19 (OR, 5.05 [95% CI, 1.82–13.96]),[23] wheezing (OR, 1.67 [95% CI, 1.23–2.15]),[24] and myocardial infarction (OR, 1.79 [95% CI, 1.20–2.66]).[25] Furthermore, dual use of e-cigarettes and cigarettes has been associated

**Table 1. E-Cigarette Disease Epidemiology**

| Design/location, year | Patient population, n | Findings |
|---|---|---|
| Respiratory symptoms and disease | | |
| Asthma | | |
| Cross-sectional analysis/South Korea, 2016[18] | 35 904 high school students | Prevalence rate of asthma was 3.9% in current e-cigarette users, 2.2% in former e-cigarette users, and 1.7% in never e-cigarette users; AOR for asthma for current e-cigarette users was 3.41 (95% CI, 1.79–6.49) |
| Cross-sectional analysis/United States, 2019[19] | 402 822 never combustible cigarette smoker adults (>18 y); current e-cigarette users, 3103 (0.8%); 8.5% had asthma; median age group of current e-cigarette users was 18 to 24 years | Current e-cigarette use was associated with higher odds of self-reported asthma compared with never e-cigarette use (OR, 1.39 [95% CI, 1.15–1.68]) |
| Chronic bronchitis (chronic cough, phlegm, wheeze, or bronchitis) | | |
| Cross-sectional study/California, 2017[20] | 2086 youth (11th and 12th grade) | Risk of bronchitis symptoms was higher among past users (OR, 1.85 [95% CI, 1.37–2.49]) and current users (OR, 2.02 [95% CI; 1.42–2.88]) compared with never-users |
| Cross-sectional analysis/Hawaii, 2019[21] | 8087; mean age 55 years | E-cigarette use was associated with chronic pulmonary disorder (AOR, 2.58 [95% CI, 1.36–4.89]; $P<0.01$) |
| Other respiratory symptoms | | |
| Longitudinal analysis/United States, 2020[22] | 46 000; age ≥12 years | Associations between former e-cigarette use (AOR, 1.31 [95% CI, 1.07–1.60]) or current e-cigarette use (AOR, 1.29 [95% CI, 1.03–1.61]) and respiratory disease; current combustible tobacco smoking (AOR, 2.56 [95% CI, 1.92–3.41]) was also associated with having respiratory disease |
| Cross-sectional study/United States, 2020[24] | 28 171 adults: 641 (1.2%) current exclusive e-cigarette users, 8525 (16.6%) current exclusive smokers, 1106 (2.0%) dual users, 17 899 (80.2%) nonusers | Incidence of wheezing and related respiratory symptoms was higher in current e-cigarette users (AOR, 1.67 [95% CI, 1.23–2.15]) compared with nonusers; current e-cigarette users had lower risk of wheezing and related respiratory symptoms compared with current smokers (AOR, 0.68 [95% CI, 0.53–0.87]) |
| Cardiovascular disease | | |
| Cross-sectional analysis/United States, 2018[25] | 69 725 adults (>18 y) | Daily e-cigarette use was independently associated with higher odds of having had a myocardial infarction (OR, 1.79 [95% CI, 1.20–2.66]; $P=0.004$), as was daily conventional cigarette smoking (OR, 2.72 [95% CI, 2.29–3.24]) |
| Cross-sectional analysis/United States, 201926 | 449 092 adults (>18 y) | No association between e-cigarette use and cardiovascular disease; dual use was significantly associated with higher rates of cardiovascular disease vs smoking alone (OR, 1.35 [95% CI, 1.18–1.56]) |

AOR indicates adjusted odds ratio; and OR, odds ratio.

with higher rates of cardiovascular disease (OR, 1.36 [95% CI, 1.18–1.56])[26] and cardiovascular risk factors, including metabolic syndrome (OR, 1.57 [95% CI, 1.03 to 2.40]),[27] versus sole cigarette use. Smoking cessation aided by e-cigarettes or other noncombustible nicotine/tobacco products was recently shown to put quitters at increased risk of cardiovascular disease relative to those who quit without use of these alternatives (hazard ratio, 1.31 [95% CI, 1.01–1.70]).[28] Owing to the novelty of e-cigarettes and the rapidly changing market, these associations (excluding respiratory disease) are derived solely from cross-sectional studies and will require longitudinal surveillance for validation.

## E-Cigarettes as a Potential Smoking Cessation Tool

Evaluating the efficacy of e-cigarette use as a smoking cessation strategy (Table 2) is of utmost importance to clinicians. Clinical trials have lagged behind the rapidly evolving e-cigarette market, limiting the bulk of data to outdated first- and second-generation devices. In 2020, a Cochrane Database Systematic Review meta-analysis of 50 clinical trials and intervention studies[29] (total n=12 430) concluded that there is evidence of moderate certainty that electronic cigarettes with nicotine increase smoking cessation rates compared with electronic cigarettes without nicotine (risk ratio, 1.71 [95% CI, 1.00–2.92]) and nicotine replacement therapies (NRTs; risk ratio, 1.69 [95% CI, 1.25–2.27]).[29] The most recent update to this review includes 56 studies and 12 804 people.[30] The authors conclude with moderate confidence that nicotine e-cigarettes probably help people to stop smoking for at least 6 months and probably work better than NRT and nicotine-free e-cigarettes. They stress the need for more reliable evidence on the effects of newer e-cigarettes that have greater nicotine delivery.

The duration of cessation is a critical factor that has been examined in other studies. A United Kingdom–based trial achieved 1-year smoking abstinence rates of 18% and 9.9% for people provided with second-generation e-cigarettes or their choice of standard NRTs, respectively (n=886).[31] All patients also received counseling for a minimum of 4 weeks. Although e-cigarettes

**Table 2. Findings From E-Cigarette Smoking Cessation Studies**

| Design, location, year | Sample size/patient population | Device generation | Findings |
|---|---|---|---|
| Meta-analysis, 2020[29] | 50 studies representing 12 430 patients; 26/50 were randomized clinical trials | NA | Use of electronic cigarettes with nicotine improves smoking cessation rates compared with electronic cigarettes without nicotine (RR, 1.71 [95% CI, 1.00–2.92]) and NRTs (RR, 1.69 [95% CI, 1.25–2.27]) |
| Meta-analysis, 2016[35] | 20 studies representing 40 815 individuals; 2/20 were randomized clinical trials with 757 patients combined | NA | The odds of quitting cigarettes were 28% lower (OR, 0.72 [95% CI, 0.57–0.91]) in those who used e-cigarettes compared with those who did not; data were driven by observational studies, as the 2 clinical trials collectively showed no change in cessation rates |
| Meta-analysis, 2017[34] | 12 studies representing 14 122 individuals; 3/12 were randomized clinical trials with 1007 patients combined | NA | The odds of quitting cigarettes were 26% lower (OR, 0.74 [95% CI, 0.55–1.0]) in those who used e-cigarettes compared with those who did not; results were of low certainty on the basis of the the Grading of Recommendations Assessment, Development and Evaluation approach |
| Randomized clinical trial, United Kingdom, 2019[31] | 886 patients from UK stop-smoking services; largely middle-aged smokers, median age 41 years | 2nd | 1-year smoking abstinence rates were significantly higher (18%) for the e-cigarette group compared with 9.9% in the NRT group (RR, 1.83 [95% CI, 1.30–2.58]); patients in the e-cigarette group were more likely to still be using e-cigarettes (80%) than subjects who were treated with NRT (9%) after 1 year; 25% of participants in the e- cigarette group became dual users |
| Randomized clinical trial, Canada, 2020[33] | 376 patients with a moderate to strong desire to attempt to quit; mean age 52 years | 2nd | 12-week smoking abstinence rates were significantly higher for the nicotine e-cigarette group with counseling (21.9%) vs counseling alone (9.1%); abstinence rates for the nicotine-free e-cigarette group with counseling were not significantly higher (17.3%) than counseling alone |
| Randomized intervention trial, United States, 2018[36] | 6006 smokers from 54 US companies; median age 44 years | Unclear | 6-month smoking abstinence rates were not significantly different in the e-cigarette group (1.0%) with standard care (free motivational text messaging and information about the benefits of cessation) versus the NRT group (0.5%) with standard care or standard care alone (0.1%) |

NRT indicates nicotine replacement therapy; OR, odds ratio; and RR, risk ratio.

were effective smoking cessation tools, participants using them were much more likely to still be using e-cigarettes (80%) than participants who were treated with NRTs (9%) after 1 year. Furthermore, 25% of participants in the e-cigarette group became dual users, although dual users in the e-cigarette group experienced greater reductions in cigarette use than dual NRT/cigarette users. These caveats have led other groups to argue against e-cigarette use as a first-line treatment option, owing to the lack of comparable efficacy in nicotine cessation and the potential for e-cigarette–induced harm during or after cigarette cessation.[32] A recent Canadian trial (n=376) using second-generation devices found that providing a nicotine-containing e-cigarette with counseling versus counseling alone significantly increased smoking abstinence rates at 12 weeks (21.9% versus 9.1%, respectively), whereas nicotine-free e-cigarettes did not (17.3%). However, this study did not include an NRT comparison group, and early termination limited statistical power of the trial.[33]

Outside of clinical settings, the effects of vaping on smoking cessation seem less favorable.[34–37] The most recent meta-analysis that included observational studies regarding e-cigarette use and smoking cessation was published in 2021 and used studies published through January 2020.[37] This meta-analysis included 55 observational studies and 9 randomized clinical trials. Analysis of clinical trial data corroborated the Cochrane Database Systematic Review,[29] showing an association between e-cigarette use and smoking cessation (OR, 1.53 [95% CI, 1.16–2.02]). However, the observational study data showed that e-cigarette use was not associated with smoking cessation in adult smokers (OR, 0.95 [95% CI, 0.77–1.16]) or in a subset of adult smokers who were motivated to quit smoking (OR, 0.85 [95% CI, 0.68–1.06]). Similar to these observational study metadata, a randomized intervention trial of smokers (n=6006) used by 54 companies found that providing free e-cigarettes alongside standard care (free motivational text messaging and information about the benefits of cessation) was not more effective than other free cessation aids with standard care or standard care alone.[36] Unlike other randomized trials that provided evidence for e-cigarettes as effective smoking cessation aids,[31,33] this study was not carried out in a clinical setting and participants did not have access to in-person behavioral support.

The apparent dichotomy between the success of clinical trials and lack of efficacy in observational studies may be attributable in part to the behavioral support and counseling provided during clinical trials. Other variables that may contribute to variable quit rates include nicotine concentration and users' previous experience with vaping, which have both been shown to be significant predictors of success.[38,39] Whereas these referenced studies did not directly assess smoking or nicotine cessation, their findings suggest that training naive e-cigarette users to use their e-cigarettes properly could improve initial efficacy after clinical recommendations or device provision.

In part on the basis of the evidence reviewed here, the US Preventative Services Task Force has concluded that the data are insufficient to recommend e-cigarette use for smoking cessation in adults.[40] In the 2020 *Smoking Cessation: A Report of the Surgeon General*,[41] a comparable conclusion was reached that the evidence is inadequate to infer that e-cigarettes increase smoking cessation. However, the report suggests that the use of e-cigarettes containing nicotine was associated with increased smoking cessation compared with the use of nicotine-free e-cigarettes. E-cigarettes are not approved by the Food and Drug Administration as an aid for quitting tobacco cigarette use. Outside of clinical studies, the use of e-cigarettes for smoking cessation is not supported and should not be recommended to patients. Smoking cessation trials using third- and fourth-generation e-cigarettes that deliver greater amounts of nicotine are needed; studies should include both smoking and nicotine cessation as e-cigarette efficacy end points.

## Pathophysiology

### *Clinical Study Issues*

To evaluate the acute effects of vaping, most of the clinical trials assessed in this review used randomized, crossover designs with substantial washout periods. Because e-cigarette research is still in its early stages, long-term prospective cohort studies evaluating the risks of chronic use are unavailable. Furthermore, the development of new e-cigarettes has outpaced the research. The bulk of studies have examined use of first- or second-generation e-cigarettes (see Figure 1), which differ substantially from modern devices in terms of electronic power, nicotine strength, and popularity. The results of trials with these devices may not translate or be relevant to newer devices that can deliver higher amounts of nicotine. Because of the novelty of e-cigarettes, clinical guidelines and decision-making must be informed by clinical, observational, and laboratory studies; however, many key studies have not yet been performed.

### *E-Cigarette Effects on the Cardiovascular System*

#### *Effects of Vaping on Sympathetic Activation of the Cardiovascular System*

The effects of vaping on heart rate and blood pressure have been extensively studied (Table 3). Despite using different e-cigarette device types (generations 1–3), nicotine concentrations, and instructions for user inhalation, 5 of 7 studies found that vaping with nicotine caused significant acute increases in both heart rate and blood pressure (n=15–70).[42–48] One study demonstrated significant increases during nicotine-free vaping, an effect that did not persist for long after the vaping session.[43] ECG measurements revealed that vaping shifted heart rate variability toward sympathetic predominance.[49,50]

**Table 3. Effects of E-Cigarette Use on the Cardiovascular System**

| Condition | Biomarker | Change | Device generation | Nicotine concentration, mg/mL | Flavor | Sample size, n |
|---|---|---|---|---|---|---|
| Acute E-cigarette use, clinical trials | | | | | | |
| Sympathetic effects | HR | ↑[42–47] | 1st,[44] 2nd,[45,47] 3rd[42,43,46] | 0,[43] 1.5,[46] 3,[43] 18,[47] 24,[42] several[44] unclear[45] | None,[43,46] tobacco,[42,45,47] several[44] | 15,[42] 20,[45,47] 23,[44] 25,[43] 30[46] |
| | | No change[44,46,48] | 1st,[44] 2nd,[48] 3rd[46] | 0,[46,48] 12,[48] several[44] | None,[46] several,[44] unclear[48] | 23,[44] 30,[46] 70[48] |
| | Systolic BP | ↑[42–46] | 1st,[44] 2nd,[45] 3rd[42,43,46] | 0,[43,46] 1.5,[46] 3,[43] 24,[42] several,[44] unclear[45] | None,[43,46] tobacco,[42,45] several[44] | 15,[42] 20,[45] 23,[44] 25,[43] 30[46] |
| | | No change[44,47,48] | 1st,[44] 2nd[47,48] | 0,[48] 12,[48] 18,[47] several[44] | Tobacco,[47] several,[44] unclear[48] | 20,[47] 23,[44] 70[48] |
| | Diastolic BP | ↑[43–45] | 1st,[44] 2nd,[45] 3rd[43] | 0,[43] 3,[43] several,[44] unclear[45] | None,[43] tobacco,[45] several[44] | 20,[45] 23,[44] 25[43] |
| | | No change[42,46–48] | 2nd,[47,48] 3rd[42,46] | 0,[46,48] 12,[48] 18,[47] 24[42] | None,[46] tobacco,[42,47] unclear[48] | 15,[42] 20,[47] 30,[46] 70[48] |
| | Tone | Sympathetic ↑, vagal ↓[49] | 2nd | 12 | Strawberry | 33 |
| | HRV | ↓[105] | 1st (2nd-hand exposure) | 1.8 | None | 5 |
| Vascular stiffness | PWV | ↑[42,43,48] | 2nd,[48] 3rd[42,43] | 0,[48] 3,[43] 12,[48] 24[42] | None,[43] tobacco,[42] unclear[48] | 15,[42] 25,[43] 70[48] |
| | | No change[43] | 3rd | 0 | None | 25 |
| | AIx | ↑[42,43,48] | 2nd,[48] 3rd[42,43] | 0,[48] 3,[43] 12,[48] 24[42] | None,[43] tobacco,[42] unclear[48] | 15,[42] 25,[43] 70[48] |
| | | No change[43] | 3rd | 0 | None | 25 |
| Endothelial function | No bioavailability | ↑[45,61] | 2nd,[45] unclear[61] | Unclear[45, 61] | Tobacco[45,61] | 20,[45] 40[61] |
| | FMD | ↓[45,55,61] | 1st,[55] 2nd,[45] unclear[61] | 0,[55] unclear[45,61] | Tobacco,[45,61] unclear[55] | 20,[45] 31,[55] 40[61] |
| Endothelial damage | EPCs | ↑[64] | 2nd | 12 | None | 16 |
| | Endothelial microvesicles | ↑[63] | 3rd | 19 | None | 17 |
| | | No change[47,63,64] | 2nd,[47,64] 3rd[63] | 0,[63] 12,[64] 18[47] | None,[63,64] tobacco[47] | 16,[64] 17,[64] 20[47] |
| Oxidative stress | MPO | ↑[43] | 3rd | 3 | None | 25 |
| | | No change[43] | 3rd | 0 | None | 25 |
| | H2O2 | ↑[45] | 2nd | Unclear | Tobacco | 20 |
| | sNOX2-dp | ↑[45,61] | 2nd,[45] unclear[61] | Unclear[45, 61] | Tobacco[45,61] | 20,[45] 40[61] |
| | 8-iso-PGF2α | ↑[45,61] | 2nd,[45] unclear[61] | Unclear[45, 61] | Tobacco[45,61] | 20,[45] 40[61] |
| | MDA | ↑[48] | 2nd | 0, 12 | Unclear | 70 |
| | LDL-Ox, PON1, HOI | No change[49] | 2nd | 12 | Strawberry | 33 |
| Thrombotic effects | Platelet aggregation | ↑[70] | Unclear | Unclear | Tobacco | 40 |
| | sP-selectin | ↑[45, 70] | 2nd, unclear[70] | Unclear[45, 70] | Tobacco[45,70] | 20,[45] 40[70] |
| | sCD40L | ↑[45,70] | 2nd,[45] unclear[70] | Unclear[45, 70] | Tobacco[45,70] | 20,[45] 40[70] |
| | Platelet-derived microvesicles | ↑[47,63] | 2nd,[47] 3rd[63] | 18,[47] 19[63] | None,[63] tobacco[47] | 17,[63] 20[47] |
| | | No change[63] | 3rd | 0 | None | 17 |
| Myocardial effects | Systolic and diastolic function | No change[72] | 2nd | 11 | None | 36 |
| Observational studies | | | | | | |
| Condition | Biomarker | Change | Participant characteristics | | | |
| Sympathetic effects | HR | No change[58] | E-cigarette users (n=36), cigarette smokers (both >4 days/week; n=285) vs nonuser controls (n=94) | | | |
| | Systolic BP | | | | | |
| | Diastolic BP | | | | | |

(*Continued*)

**Table 3. Continued**

| Condition | Biomarker | Change | Participant characteristics |
|---|---|---|---|
| | Tone | Sympathetic ↑[50] | Habitual e-cigarette users (>1 year; n=16) vs nonuser controls (n=18) |
| | | Vagal ↓[50] | |
| Vascular stiffness | PWV | No change[58] | E-cigarette users (n=36), cigarette smokers (both >4 days/week; n=285) vs nonuser controls (n=94) |
| | AIx | ↑*[58] | |
| Oxidative stress | LDL-Ox | ↑[50] | Habitual e-cigarette users (>1 year; n=16) vs nonuser controls (n=18) |
| | PON1 | No change[50] | |
| | HOI | No change[50] | |
| | 8-iso-PGF2α | No change[68] | E-cigarette users (n=261) vs nonuser controls (n=2191) |

Reference groups for all studies were either baseline measures or within-subjects sham vaping/smoking control. AIx indicates augmentation index; BP, blood pressure; EPC, endothelial progenitor cell; FMD, flow-mediated dilation; HOI, high-density lipoprotein antioxidant index; HR, heart rate; HRV, heart rate variability; LDL-Ox, low-density lipoprotein oxidation; MDA, malondialdehyde; MPO, myeloperoxidase; NO, nitric oxide; PGF2α, prostaglandin F2α; PON1, paraoxonase 1; PWV, pulse wave velocity; sCD-40 L, soluble CD-40 ligand; sNOX2-dp, soluble NOX2-derived peptide; and sP-selectin, soluble P-selectin.

*Significant difference across groups using analysis of variance; post hoc of e-cigarette vs nonuser control not provided.

These results collectively suggest that use of nicotine-containing e-cigarettes causes sympathetic activation of the cardiovascular system, which could pose long-term health risks for chronic users or exacerbate preexisting cardiopulmonary conditions.[51,52]

### *Effects of Vaping on Vascular Health*

Arterial stiffening has been validated as a reliable, independent predictor of adverse cardiovascular outcomes and all-cause mortality.[53] Arterial stiffening contributes to the development of heart failure and is closely linked to atherosclerosis pathogenesis.[54] The rate at which pressure waves propagate through arteries (pulse wave velocity [PWV]) is a clinically relevant indicator of arterial stiffness. Several studies showed that acute e-cigarette use increased PWV, with increases ranging from 0.19 m/s to 0.80 m/s (n=15–70).[42,43,48,55] Significant increases in PWV that were both nicotine-dependent (n=35)[48] and nicotine-independent (n=35, n=31) were detected.[48,55] Owing to the rapid time frame of these trials, increases in PWV are likely the result of sympathetic modulation of smooth muscle tone or endothelial dysfunction (discussed

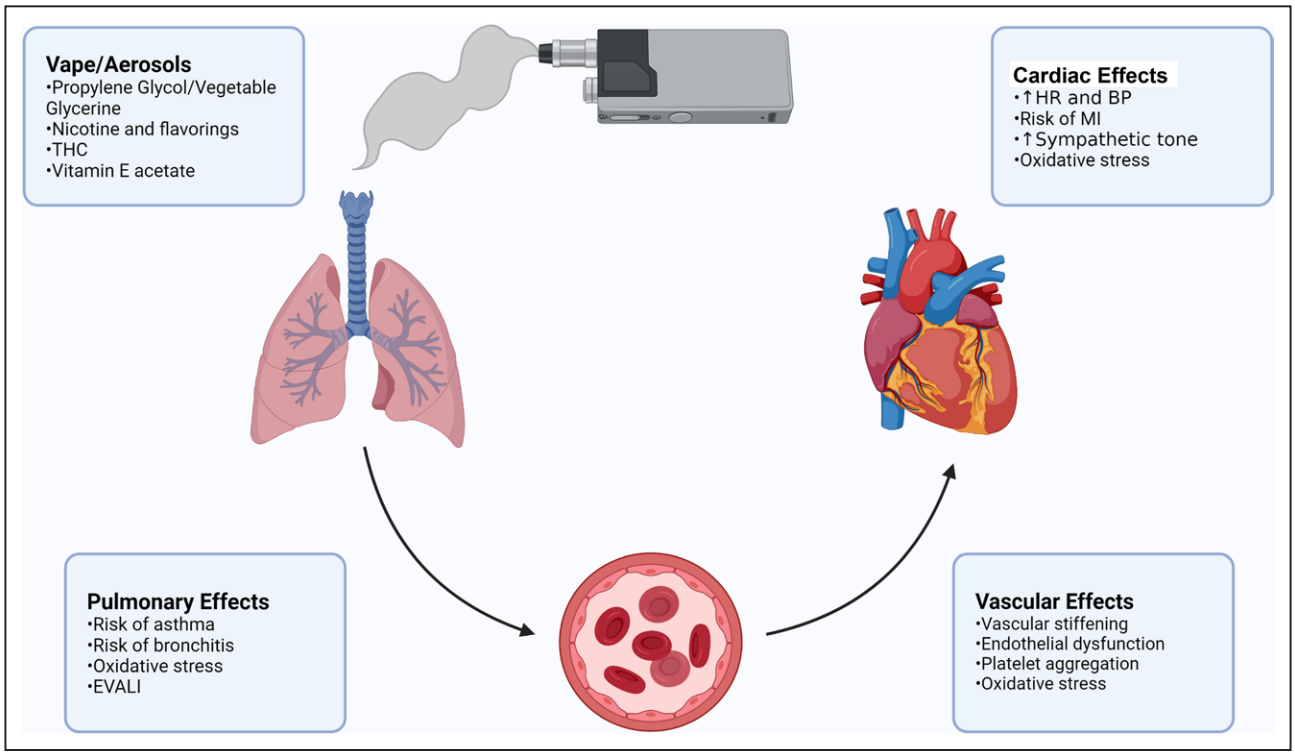


**Figure 2. Schematic of cardiopulmonary effects of e-cigarette use.**
Schematic representing the cardiopulmonary effects of various aerosols from e-cigarette vapor and potential concerns for clinicians. Created with BioRender.com. BP indicates blood pressure; EVALI, e-cigarette or vaping product use–associated lung injury; HR, heart rate; MI, myocardial infarction; and THC, tetrahydrocannabinol.

in the following) as opposed to vascular remodeling.[56,57] A 2020 cross-sectional study (n=36 e-cigarette users, 285 smokers, and 94 nonuser controls) found that e-cigarette and cigarette users showed no difference in adjusted PWV versus nonusers.[58] However, elsewhere, cigarette use has been associated with increased PWV,[59] highlighting the need for more long-term observational cohort studies with e-cigarette users. The effects of chronic vaping on clinically relevant cardiovascular stiffness end points remain speculative and require further study.

Depletion of vasodilatory nitric oxide is a widely accepted driver of endothelial and vascular dysfunction.[60] Several studies reported significant decreases (27% to 31%) in nitric oxide bioavailability or nitric oxide metabolite concentrations in patient plasma after acute vaping (n=10–40).[45,61,62] Studies also demonstrated reductions in vasodilatory function after acute e-cigarette use.[43,45,55,61] Reductions in stimulated nitric oxide production from e-cigarette user endothelial cells were also observed in a cross-sectional observational study; however, no differences in baseline flow-mediated dilation were reported between groups (n=36 e-cigarette users, 285 smokers, and 94 nonuser controls).[58] In addition to reductions in endothelial function, acutely elevated biomarkers of endothelial damage have been observed in patient serum after vaping (n=10–40).[61,63–65]

Oxidative stress underlies multiple cardiovascular disorders and is known to deplete nitric oxide and induce endothelial cell damage.[66,67] Clinical and observational trials of acute e-cigarette inhalation ± nicotine found significant increases in biomarkers of oxidative stress (n=10–70).[43,45,48,50,61,62]

Overall, vaping acutely altered the human vasculature, likely as a result of sympathetic modulation and oxidative stress. Although the long-term consequences of e-cigarette use on vascular health remain to be determined, there are reasonable grounds for concern that chronic vaping may impair vascular function in never-smokers. However, when compared with traditional cigarette smoking, some studies found that acute vaping caused less pronounced effects on vascular function and oxidative stress (n=20–70).[45,48,61] A recent large-scale observational study (n=2191 nonusers, 261 e-cigarette users, 3261 smokers, and 1417 dual users) found that both dual use and exclusive cigarette use were significantly associated with higher levels of inflammatory and oxidative stress biomarkers in blood, whereas exclusive e-cigarette use was not.[68] Furthermore, a 2019 trial (n=114) found that switching from traditional cigarettes to a first-generation e-cigarette for 1 month led to a clinically significant improvement in flow-mediated dilation (1.49% [95% CI, 0.93–2.04%]) and a significant decrease in PWV (−0.53 [95% CI, −0.95 to −0.11]).[69] Overall, these findings suggest that from a vascular perspective, exclusive vaping has a profile of reduced harm when compared with cigarette smoking.

### *Associations Between Vaping and Prothrombotic Biomarkers*

Studies have indicated that vaping acutely induces platelet aggregation and activation.[45,47,63,70,71] These studies generally found that e-cigarettes have less pronounced effects on biomarkers of platelet activation and aggregation than traditional cigarettes.[45,70] Considering the importance of platelet activation in cardiovascular disease states, including thrombosis, atherosclerosis, and myocardial infarction, the potential consequences of chronic e-cigarette use on this aspect of cardiovascular physiology require further study.

### *Assessment of Myocardial Health in E-Cigarette Users*

Over time, traditional cigarette smoking increases the risk of cardiovascular diseases including hypertension, atherosclerosis, and heart failure, suggesting that these outcomes should be monitored in chronic e-cigarette users.[51,52] Survey data showed that daily e-cigarette use was independently associated with higher odds of myocardial infarction (OR, 1.79 [95% CI, 1.20–2.66]; n=69 725).[25] Whereas this study is limited by its cross-sectional design and requires longitudinal studies for validation, the findings underscore the importance of monitoring for secondary myocardial alterations that can occur after chronic pulmonary and vascular changes. To date, only 1 study has investigated the potential acute effects of e-cigarette use on myocardial function in adult smokers using echocardiography, and reported no changes (n=36).[72] However, acute or short-term studies are not likely to detect cardiac remodeling, and thus are not a proxy for long-term studies. Clinical trials and prospective studies investigating the effects of e-cigarette use on myocardial function have not yet been performed.

A shift in cardiac autonomic balance toward increased sympathetic drive,[73] increased oxidative stress,[74] increased vascular stiffness,[53] and endothelial dysfunction[75] associates with increased cardiovascular morbidity and mortality. The evidence reviewed regarding the cardiovascular effects of e-cigarettes is based on studies of small sample sizes, with limited clinical follow-up. Large-scale studies designed to dissect the mechanisms by which e-cigarettes convey potential cardiovascular harm are needed to assess the safety of e-cigarettes. The 2019 American College of Cardiology/American Heart Association guideline on primary prevention of cardiovascular disease recommends that clinicians ask all adults about e-cigarette use.[76] E-cigarettes are not recommended for tobacco cessation treatment.

## *E-Cigarette Effect on the Respiratory System*

Pharmacokinetics have not yet been performed on e-cigarette constituents in the lung. However, it is estimated that nicotine levels are ≈200 times higher in the lungs than at peak systemic levels after both smoking and vaping.[77] Chronic tobacco smoking damages the lung's

ultrastructure and erodes innate immunity, leading to higher incidence of chronic obstructive pulmonary disease and lung cancer (Table 4). It is not known whether vaping will produce lung disease, but bronchitis, alveolar damage, decreased immunity to infection, and wheezing are potential symptoms to be monitored in chronic e-cigarette users. Regarding lung function, differences between nonsmokers and smokers are relatively small

**Table 4. Effects of E-Cigarette Use on the Respiratory System**

| Design, year | Patient population | Device type/study duration | Findings |
|---|---|---|---|
| Acute studies assessing lung function | | | |
| Double-blinded crossover study, 2019[106] | 17 occasional smokers, 6 male, mean age 26 | 3rd-generation | Acute increase in flow resistance, indicating obstruction of the conducting airways |
| Randomized clinical trial, 2018[94] | 23 occasional smokers, 16 male, mean age 23 | 3rd-generation | Tissue hypoxia and lower airway injury |
| Laboratory-based study, 2015[80] | 20 smokers (10) and nonsmokers (10), mean age 39 | 1st-generation | No immediate adverse effects of nicotine-free vaping on nonsmokers and only small effects on FEV1 and FEF25 in smokers |
| Laboratory-based study, 2012[85] | 30 smokers, 14 men, mean age 35 | 1st-generation | Increased respiratory impedance and resistance, likely indicative of airway bronchoconstriction |
| Repeated-measures controlled study, 2013[107] | 30 smokers (15) and never-smokers (15), 16 male, age 18–57 | 2nd-generation | 1-hour tobacco smoking but not e-cigarette vaping transiently reduced lung function |
| Crossover and placebo-controlled trial, 2017[82] | 20 (healthy, 20–37 y) and 10 (asthma, 21–40 y) | Unclear | 1-hour vaping session of propylene glycol/glycerol did not significantly affect pulmonary function in healthy or asthmatic subjects |
| Acute studies assessing lung health biomarkers and -omics approaches | | | |
| Single-blind within-subjects study, 2019[93] | 25 smokers, 18 male, mean age 23 | 3rd-generation | Increased biomarker of airway epithelial injury (serum CC16), sustained decrement in transcutaneous oxygen tension and impaired arterial oxygen tension |
| Randomized, investigator-blinded, 3-period crossover study, 2020[46] | 30 male e-cigarette users who were former smokers, mean age 38 | 3rd-generation | Decreased lung inflammation, increased biomarker of airway epithelial injury (serum CC16), decreased transcutaneous O2 tension |
| Pilot clinical trial, 2020[108] | 30 never-smokers, male and female, age 21–30 | 3rd-generation; 4-week intervention period | E-cigarette use and inhalation correlated with change in cell counts (macrophages and lymphocytes) and cytokines (IL-8, IL-13, and TNF-α); no significant changes in mRNA or miRNA gene expression |
| Cohort studies, 2018[65] | 10 adult never-smokers (≥21 y), 5 female | 1st-generation | Altered transcriptomes of small airway epithelium and alveolar macrophages for all participants after inhalation of e-cigarette with nicotine |
| Observational studies | | | |
| Observational, cross-sectional study; sputum collection, 2018[95] | 44 adults (≥18 y); 14 current cigarette smokers, 15 current e-cigarette users, and 15 never-smokers | NA | Increases in aldehyde detoxification and oxidative stress–related proteins associated with cigarette smoke; innate defense proteins associated with COPD, including MUC5AC, were elevated in e-cigarette users; increases in neutrophil granulocyte-related and NET-related proteins |
| Observational, cross-sectional study; research bronchoscopies, 2018,[84] 2019[77] | 41/42 healthy adults (>21 y), 19/20 female | NA | Vape airways appeared friable and erythematous; 113 uniquely altered proteins in e-cigarette users' airways; MUC5AC elevated in e-cigarette users; neutrophil elastase, MMP-2, and MMP-9 activities and protein levels were equally elevated in both e-cigarette users' and smokers' BAL relative to nonsmokers |
| E-cigarette assisted cessation trials | | | |
| Randomized controlled trial, 2019[88] | 263 smokers, 111 male, mean age 47 | 1st-generation; 3- month cessation trial | No changes in standard spirometry |
| Randomized controlled trial, 2017[86] | 105 smokers, 68 male, mean age 38 | 1st-generation; 5 day cessation trial | No changes in standard spirometry |
| Randomized controlled trial, 2016[87] | 130, 190 male, mean age 44 | 1st-generation; 1 yr cessation trial | No changes in most standard spirometry measures, improvement in FEF25%–75% among quitters |

BAL indicates bronchoalveolar lavage; CC16, club cell protein 16; FEF25, forced expiratory flow at 25%; IL, interleukin; eCO, exhaled carbon monoxide; FeNO, fractional exhaled nitric oxide; miRNA, microRNA; MMP, matrix metalloprotease; mRNA, messenger RNA; NET, neutrophil extracellular trap; and TNF-α, tumor necrosis factor–α.

at young ages (ie, 20–40 years) but become more significant over time (at 40–69 years of age).[78] Thus, care must be taken when interpreting lung function measurements after e-cigarette use, and the time frames over which changes in lung function were captured must be factored into analysis. On the basis of a review of the literature (Table 4), it appears that the majority of published clinical trials on e-cigarettes have not been of sufficient duration to detect significant differences in lung function between groups.

### *Effects of Vaping on Lung Function*

Smoking cessation has been shown to halt the decline in lung function caused by combustible tobacco product use, but does not restore lung function.[79] Whether or not e-cigarette use is less harmful than conventional cigarette smoking is controversial (Table 4). Randomized clinical trials of acute and chronic e-cigarette use have shown variable results, with some showing reductions in lung function measured using spirometry[80,81] and others showing no change.[77,82–84] Using impulse oscillometry, which measures both small and large airway resistance and is more sensitive than standard spirometry, Vardavas et al[85] found elevated impedance in smokers after acute vape sessions (n=30). Owing to the rapid time frame, these changes were likely attributable to airway smooth muscle contraction (bronchoconstriction) rather than to lung damage.

In one study, there was no change in spirometry 5 days after switching from smoking to vaping of first-generation e-cigarettes (n=105).[86] Similarly, cigarette users who switched to vaping first-generation e-cigarettes saw no improvement after 12 months (n=183),[87] and in a randomized controlled trial where smokers were provided with either e-cigarettes or a nicotine-free cigarette substitute, no changes were detected between the 2 groups after 3 months (n=263).[88] These 2 studies did not include control groups who continued to smoke cigarettes. Collectively, switching from smoking to vaping did not provide short-term benefits, and longer trials with appropriate control arms are needed to determine whether switching from smoking to vaping can improve lung function.

The studies were all performed on healthy nonsmokers or smokers. A number of individuals who have asthma, chronic obstructive pulmonary disease, or other diseases also use e-cigarettes or switch from smoking to e-cigarettes.[89] Whereas it is known that smoking cessation is beneficial and mitigates chronic declines in lung function,[90] a 24-month longitudinal study found that switching from smoking to vaping had no effect on spirometry in asthmatic smokers (n=18).[91] Analysis of 2 observational cohorts (COPDGene, n=3536; SPIROMICS, n=1060) found that e-cigarette use was not associated with improved lung function in chronic obstructive pulmonary disease, and instead showed higher prevalence of both chronic bronchitis and acute exacerbations.[92] This was a longitudinal study; however, it was observational in nature and more studies are needed to validate or refute this finding. Collectively, these data indicate that switching from smoking combustible tobacco to vaping does not improve lung function/respiratory health in patients with preexisting lung conditions.

### *Assessment of Lung Damage in E-Cigarette Users*

In a series of randomized clinical trials, an increase in the lung damage biomarker CC16 (club cell protein 16) was detected in serum after acute exposure to e-cigarettes ± nicotine (n=30, 25, and 23).[46,93,94] Two hours after e-cigarette exposure, 71 genes were significantly altered in airway biopsies and 27 genes were altered in primary alveolar macrophages, suggesting that vaping can elicit rapid responses in the lungs.[65] The effects of long-term vaping on pulmonary gene/protein expression remain understudied. However, proteomic analysis indicated that more proteins were uniquely changed in e-cigarette users' sputum (n=66) than in smokers' sputum (n=29) relative to healthy nonsmokers (n=15 e-cigarette users, 14 smokers, and 15 nonsmoker controls).[95] A number of innate defense proteins were altered.[95] Similarly, neutrophil elastase and matrix metalloproteases, which predispose lungs to damage, were equally elevated in smokers' and e-cigarette users' bronchoalveolar lavage samples (n=14 per group).[77] Proteomic analysis of bronchial epithelial brush biopsies identified uniquely altered proteins in e-cigarette users' lungs including mucins, calcium signaling–related proteins, and xenobiotic metabolizing proteins (n=10 e-cigarette users, 13 smokers, 18 nonuser controls).[84] These studies also found comparable increases in MUC5AC mucin levels in bronchial brush biopsies and sputum from both e-cigarette users and smokers relative to nonsmokers.[84,95] Increases in expression levels of gel-forming mucins such as MUC5AC are predictive of chronic obstructive pulmonary disease severity.[96] Pulmonary function was normal across all groups,[84,95] which underscores the need for more sensitive assays beyond spirometry to assess lung function in healthy e-cigarette users. Lung imaging using computed tomography or other techniques may be useful in this regard but has not been tested in healthy e-cigarette users.

### *E-Cigarette or Vaping Product Use–Associated Lung Injury*

EVALI is a point-source epidemic, multiorgan syndrome characterized by lung injury, gastrointestinal, and other symptoms. Computed tomography scans of lungs in patients with EVALI showed diffuse ground-glass opacities, diffuse alveolar damage, interlobular septal thickening, and scarring of lower lobes, with sparing of the periphery.[97] EVALI increased from a weekly mean of 4 visits per 1 million in January 2017 to 116 visits per 1 million in autumn 2019.[98] As of February 20, 2020, a total of 2880 EVALI cases[99] and 68 EVALI-associated deaths

were reported in the United States[100]; data collection then ceased because of the COVID-19 pandemic. A total of 82% to 86% of patients reported using THC-containing products; 14% used nicotine-based e-liquids but did not report THC use (n=2668).[99] One report found that vitamin E acetate was present in the bronchoalveolar lavage of 48/51 patients with EVALI across 16 US states.[101] Thus, physicians should inquire about tetrahydrocannabinol (THC) use history in presenting patients. Vitamin E acetate is commonly used as a thickening agent in THC vaping products. In mice, vitamin E acetate exposure induced inflammation and increased the number of lipid-laden macrophages characteristic of EVALI.[102] These findings suggest that vape products containing vitamin E acetate are likely to be the causative agents of most EVALI symptoms and may also synergize with other harmful additives. Other harmful constituents found in e-liquids are trace metals such as cadmium, silicon, copper, nickel, and lead; although their contribution to EVALI remains uncertain, they may pose potential risks to e-cigarette users.[103,104] Owing to challenges in diagnosis, the Centers for Disease Control and Prevention recommended approach for patients with suspected EVALI begins with examination of symptoms and assessment of e-cigarette or vape history and use within 90 days. THC history should also be assessed, but not all e-cigarette users may recognize this name and for some patients, slang names for THC should be tried (eg, dab).

## LIMITATIONS AND FUTURE DIRECTIONS

This review has several limitations. First, clinical trials examining the effects of vaping on cardiopulmonary health are heterogeneous and many were conducted over too short a time frame to fully address the clinically important questions related to morbidity and mortality. Larger longitudinal studies with clinical follow-up will be crucial to determine the effects of e-cigarette use on cardiovascular health and inform guidelines for use of e-cigarettes as a smoking cessation tool. Second, studies assessing the effects of e-cigarettes on lung function were too short of a duration. Future longitudinal studies are needed to determine the effects of e-cigarette use on lung function and to assess whether lung function decline is halted when converting from conventional cigarettes to e-cigarettes. Third, the majority of studies enrolled adult smokers as opposed to younger e-cigarette users, who make up a sizeable majority of new users. Adult smokers have the potential confounder of preexisting cardiovascular and pulmonary disease. The effect of vaping on adolescents and young adults requires further evaluation. Fourth, our search criteria were limited to English-language studies and may not have included relevant publications. In addition, knowledge gaps exist, with a lack of prospective studies assessing the effects of e-cigarettes on clinical cardiovascular outcomes.

**Table 5. Considerations for Clinicians**

| |
|---|
| • Clinicians should monitor patients not only for tobacco use, but also for e-cigarette use, and associated health problems. |
| • The use of e-cigarettes is associated with elevated cardiovascular risks and adverse effects on the lungs. |
| • The use of e-cigarettes is not safe for children, teens, young adults, pregnant women, or adults not using traditional cigarettes. |
| • The long-term health effects of the use of e-cigarettes are not known. |

## CONCLUSIONS

Observational epidemiologic studies have associated vaping with higher incidence of pulmonary disease and myocardial infarction and acute studies investigating pulmonary and cardiovascular biomarkers suggest tissue damage and compromised vascular function. Although these findings are largely limited to cross-sectional studies and short-term clinical trials, current evidence of absolute harm signals that e-cigarettes could compromise cardiovascular and respiratory health over time. Several studies assessing relative harm suggest reduced harm from vaping compared with smoking; however, harm reduction has not been noted for all outcome measures studied (eg, spirometry), and the extent of reduction in harm when smokers switch to electronic cigarettes is uncertain and requires further study. Although e-cigarettes may facilitate smoking cessation, they are not associated with a reduction in nicotine use dependency and may lead to dual use of e-cigarettes and cigarettes. Clinicians should ask about and document e-cigarette use to enable assessment of the health risks of e-cigarette use. Clinicians should also discourage nonsmokers and adolescents from using e-cigarettes and discourage smokers from engaging in dual use without cigarette reduction or cessation (Table 5).

## ARTICLE INFORMATION

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None.

## Supplemental Material

Search terms

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