Cureus

Review began 05/14/2023 Review ended 05/20/2023 Published 05/26/2023

© Copyright 2023

Rahman et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Characterization and Summarization of the Impact of Electronic Cigarettes on the Cardiovascular System: A Systematic Review and Meta-Analysis

Ali Rahman 1 , Sura Alqaisi 2 , Rana Alzakhari 3 , Sunil Saith 4

1. Internal Medicine, Northwell Health at Mather Hospital, Port Jefferson, USA 2. Internal Medicine, Memorial Healthcare, Pembroke Pines, USA 3. Internal Medicine, Richmond University Medical Center, Staten Island, USA 4. Cardiology, State University of New York Downstate Medical Center, Brooklyn, USA

Corresponding author: Ali Rahman, dr.ali_ayad@yahoo.com

Abstract

Electronic cigarettes may increase the risk of long-term cardiovascular morbidity. To protect the heart, awareness should be raised of the risks and limits of E-cigarette aerosol exposure. Thus, this systematic review and meta-analysis assessed the cardiovascular risk of e-smoking. This systematic review was conducted by using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. We searched PubMed, Embase, Scopus, Web of Science, and Science Direct databases in December 2022 to identify studies investigating e-cigarettes' impact on the heart. The study was supported by meta-analysis and qualitative review.

Out of the initial 493 papers, only 15 met the inclusion criteria and were included in the study. The cumulative number of participants in the myocardial infarction (MI) group was 85,420, and in the sympathetic groups in whom the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and heart rate (HR) were measured, were 332 cigarette smokers. The control group included the "never use," "non-smokers," and "never smoke." The pooled analysis showed a significant difference between the e-cigarette smokers and the control group regarding the risk of developing MI in former smokers (OR= 0.12; 95% CI: 0.01-1.72, P = 0.12) and never smoked (OR= 0.02; 95% CI: 0.00-0.44, P = 0.01) favoring the control group. The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers with nicotine and the control group regarding the mean difference (MD) of the SBP (MD = 2.89; 95% CI: 1.94-3.84; P < 0.001), the DBP (MD = 3.10; 95% CI: 0.42-5.78; P = 0.02), the MBP (MD = 7.05; 95% CI: 2.70-1.40; P = 0.001), and HF (MD = 3.13; 95% CI: 0.96-5.29; P = 0.005) favoring the control group. We conclude that using e-cigarettes has a detrimental effect on cardiac health. The risk of severe cardiac conditions increases with e-cigarettes are less harmful should be challenged.

Categories: Cardiology, Preventive Medicine, Substance Use and Addiction **Keywords:** heart failure, qtc interval, myocardial infarction, cardiovascular diseases, e-cigarettes, electronic cigarettes

Introduction And Background

The Centers for Disease Control and Prevention have reported that electronic cigarettes are associated with an increased risk of cardiovascular disease [1]. E-cigarette vapor includes particles that may enter the circulation and promote inflammation. These particles increase the risk of stroke, myocardial infarction (MI), and other cardiovascular events [2-3]. E-cigarettes also contain nicotine which is the main psychoactive component of e-cigarettes and is known to be a vasoconstrictor that can increase blood pressure and heart rate [4-5]. This can stress the cardiovascular system and increase the risk of heart attack and stroke [6]. In addition, some of the chemicals in e-cigarette aerosol can damage the endothelium [7], leading to a buildup of atherosclerotic plaque, which can block or reduce blood flow [8]. This can cause serious cardiovascular problems, including arrhythmias [9], stroke [10], and MI [11]. To sum up, e-cigarettes pose a significant risk to cardiovascular health, leading to long-term complications.

Nicotine is considered the main culprit in cigarette-attributed cardiovascular devastation. The hemodynamic impact of nicotine is mediated by the activation of the sympathetic nervous system with the consequent release of noradrenaline and adrenaline in excess [12]. As a result of adrenaline release, cardiac work is augmented by the stimulation of heart rate, myocardial contractility, and blood pressure [13-14]. In patients with coronary insufficiency, nicotine impairs coronary blood supply and induces coronary spasms, thus increasing the risk of myocardial ischemia [15]. Moreover, nicotine has been associated with heart failure by promoting myocardial remodeling leading to hypertrophy and fibrosis [15].

Furthermore, the nicotine-mediated catecholamine releases may contribute to fatal cardiac arrhythmias

How to cite this article

Rahman A, Alqaisi S, Alzakhari R, et al. (May 26, 2023) Characterization and Summarization of the Impact of Electronic Cigarettes on the Cardiovascular System: A Systematic Review and Meta-Analysis. Cureus 15(5): e39528. DOI 10.7759/cureus.39528

[16]. In addition, some studies suggested that nicotine can increase platelet activation and hence, the risk of arterial thrombosis [17]. There is evidence that nicotine impacts endothelial function by enhancing oxidative stress and chronic inflammation [18].

Nicotine replacement therapy (NRT) [19] provides the body with a small, controlled amount of nicotine, which helps reduce cravings and other withdrawal symptoms that occur when quitting smoking [20]. NRTs come in patches, gum, sprays, inhalers, and lozenges, and the amount of nicotine in each form varies. NRTs are designed to reduce the severity of nicotine withdrawal symptoms, allowing the user to focus on the psychological aspects of quitting smoking. NRT has been shown to double the chances of successful quitting [21] nearly. To improve quitting success rates, NRT [22] may be used with other methods, including counseling and behavioral therapy [23]. It is well-accepted that NRT has no significant health risks [24]. On the other hand, NRT seems to have favorable links with MI, mortality, and suicidal ideation [20].

There is an ongoing controversy concerning the possible hazards and advantages of e-cigarette usage. Ecigarette advocates claim that the devices may be a safer alternative to regular cigarettes and might assist smokers in quitting [25]. However, evidence shows that e-cigarette devices are hazardous and may raise the risk of cardiovascular disease [4]. Furthermore, there are worries that e-cigarettes may be a gateway for young people to conventional cigarette usage and nicotine addiction [26]. In addition, there is evidence that using e-cigarettes might lead to inhaling potentially toxic substances, such as formaldehyde and metals [27]. The possible hazards and advantages of e-cigarette usage are the subject of continuing controversy. While some claim that the devices may be a safer alternative to regular cigarettes and might assist smokers in quitting, others contend that the devices are harmful and can raise the risk of cardiovascular disease.

Review

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [19] were followed throughout the processing stages of this study. The processing stages were performed according to the Cochrane Handbook for Systematic Reviews of Interventions [22-28].

Eligibility criteria

The criteria for included studies were the following: Studies with age groups more than 18, including randomized controlled trials (RCTs), cross-sectional studies, and clinical trials; studies concerning the impact of e-cigarettes on the cardiovascular system; studies published in English; studies on humans.

The exclusion criteria encompassed the following studies: Studies on children under 18 years of age; studies on animals; non-clinical trial articles such as reviews, clinical conferences, editorials, clinical study protocols, case studies; studies concerning systems other than the cardiovascular system.

Outcomes

The primary quantitative outcomes include sympathetic system activation and MI. The secondary qualitative outcomes include heart failure and cardiac electrical conductivity presented by QTc.

Endpoints

The systematic review includes both quantitative and qualitative analysis of data.

Search strategy and study selection

PubMed, Scopus, Web of Science, Embase, and Science Direct databases were searched using relevant keywords in January 2023. The search terms include electronic cigarettes, e-cigs, e-cigarettes, ECIG, vapes, the cardiovascular system, heart failure, MI, QTc, electrocardiogram (ECG), endothelial, and sympathetic. Wildcards and operators (AND, OR, NOT) intensified the search. MeSH term searches were used when applicable.

The search results were screened, and publications were selected depending on the selection criteria. The exclusion of the publications was based first on the paper's title, then the abstract, and finally, the retrieved full text. The publications' bibliographic references were manually examined to identify any other acceptable studies that may have been overlooked in earlier phases. For further processing, data were extracted and compiled in an electronic spreadsheet. The retrieved data comprised demographic information, age groups, gender, smoking pattern (ex-smoker, e-cigarette smoker, and dual smoker), smoking mode (tobacco smoking or e-cigarette smoking), and the present morbid status vs. healthy individuals.

Quality assessment

For appraising the evidence, the quality assessment tool proposed by Hawker et al. (2002) was utilized in the current study to determine the quality of the included studies [29]. The protocol design by Hawker et al.

(2002) is composed of nine items, including abstract and title, introduction and aim, methods and data, sampling, data analysis, ethics and bias, results, transferability (generalizability), and implications (usefulness). Each item is valued as "good," "fair," "poor," and "very poor." The total and subtotal scores were presented to give a clear idea of the strength and weaknesses of each article based on the proposed criteria.

Data extraction

Data was obtained from texts, tables, and figures using Graph Grabber, version 2.0 (Quintessa, Henley-on-Thames, UK) as well as supplementary data. We focused on the outcome measures that included sympathetic system activity, including the heart rate and blood pressure, the risk of MI and heart failure, and the QTc abnormality.

Statistical analysis

This meta-analysis used the computer program Cochrane RevMan, version 5.4 (Cochrane, London, UK). The study groups include e-cigarette smoking, tobacco smoking, dual cigarette smoking, and former smokers, as well as e-cigarettes with and without nicotine. The "never use," "non-smokers," and "never smoke" are designated as the control group.

Regarding the study outcomes, the odds ratio (OR) with a 95% confidence interval (CI) was used for dichotomous variables where appropriate, while the mean difference (MD) and 95% CI were presented for continuous variables. Cochrane'sPvalues and I2were tested to examine heterogeneity among the studies [22]. The random effects model was adopted in this meta-analysis even if I2was small to meet the expected high heterogeneity. Funnel plots and the Egger regression test could not be performed due to the limited number of included trials [30]. In addition, a sensitivity analysis was performed by sequentially deleting trials to check the stability of the outcomes. No significant effect happened after completing the sensitivity analysis due to the high variation between the included studies.

Results

Literature Search Results

The initial search yielded 493 papers from four databases, including PubMed, Scopus, Web of Science, and Science Direct. Of them, 74 articles were excluded due to duplication. Subsequently, 419 papers were subject to title and abstract screening, and 274 papers were excluded because they did not meet the inclusion criteria. The remaining 145 papers underwent full-text screening. A total of 15 studies were finally included for the final quantitative and qualitative analysis: eleven papers on the sympathetic activity of the heart [7-9], [31-39], three papers on MI in individuals using e-cigarettes [39-41], one paper on heart failure in individuals using e-cigarettes [42], and two papers on QTc interval changes in individuals using e-cigarettes [9-43] (Figure 1).

Identification of new studies via databases and registers

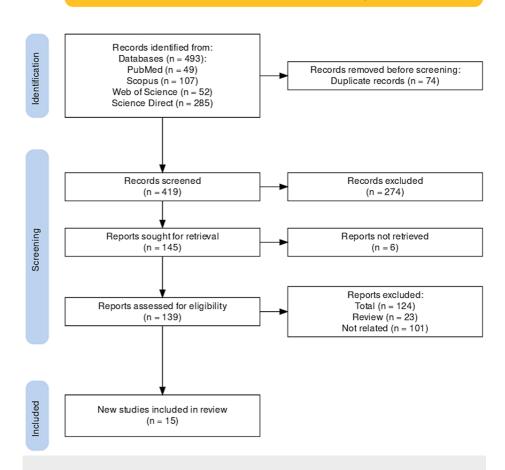


FIGURE 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Descriptive Data

The cumulative number of participants in the MI group was 85420 cigarettes smoker subdivided into four groups: current e-cigarettes smokers (n= 2663), current tobacco cigarettes smokers (n= 28481), dual cigarettes smokers (n= 8690), and former tobacco cigarettes smokers (n= 45586). The cumulative number of participants in the "sympathetic" group was 332 cigarettes smoker subdivided into four groups: current e-cigarettes smokers with nicotine (n=64), current e-cigarettes smokers without nicotine (n=64), and current e-cigarette smokers (irrespective of the nicotine contents) (n= 99), and current tobacco cigarettes smokers (n=105). The other two groups were subjected to qualitative review, including the heart failure and QTc interval groups.

Outcomes

Myocardial Infarction in Individuals Using E-cigarette Smoking

The pooled analysis of the included studies showed a significant difference between the e-cigarette and tobacco smokers regarding the risk of developing MI (OR= 0.13; 95% CI: 0.05-0.35, P < 0.001). The pooled studies were heterogeneous (I2 = 100%; P < 0.001), and the heterogeneity could not be resolved by leaving one out (Figure 2).

	electronic ci	garettes	Tobacco s	moking		Odds Ratio	Odds	Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	dom, 95% Cl				
Alzahrani 2018 [41]	41	776	4437	60100	32.7%	0.70 [0.51, 0.96]	-	-				
Critcher 2021 [40]	2262	175546	21190	175546	33.7%	0.10 [0.09, 0.10]						
Vindhyal 2020 [39]	401	16855	7291	16855	33.6%	0.03 [0.03, 0.04]						
Total (95% CI)		193177		252501	100.0%	0.13 [0.05, 0.35]						
Total events	2704		32918									
Heterogeneity: Tau ² =	0.80; Chi ² = 53	8.58, df = 2	(P < 0.0000	1); l ² = 10	0%			<u> </u>	4000			
Test for overall effect:	Z = 3.98 (P < 0	.0001)					0.001 0.1 Favours electronic cigarettes smoking	1 10 Favours Tobacco Smoking	1000			

FIGURE 2: Forest plot: odds ratio of myocardial infarction in electronic cigarette vs. tobacco smoking.

The pooled analysis of the included studies showed a non-significant difference between the e-cigarette smokers and the former smokers regarding the risk of developing MI (OR= 0.12; 95% CI: 0.01-1.72, P = 0.12). The pooled studies were heterogeneous (I2 = 100%; P < 0.001), and the heterogeneity could not be resolved by leaving one out (Figure 3).

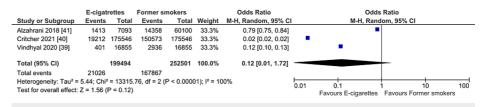


FIGURE 3: Forest plot: myocardial infarction in electronic cigarette smokers vs. former smokers.

The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers and the never smoking regarding the risk of developing MI (OR= 0.02; 95% CI: 0.00-0.44, P = 0.01). The pooled studies were heterogeneous (I2 = 100%; P < 0.001), and the heterogeneity could not be resolved by leaving one out (Figure 4).

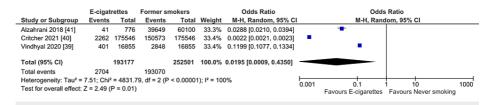


FIGURE 4: Forest plot: myocardial infarction in electronic cigarettes smokers vs. never smoking.

Sympathetic activity with e-cigarette smoking

Systolic Blood Pressure Changes in Individuals Using E-cigarettes

The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers with nicotine and the control group regarding the mean difference (MD) of the systolic blood pressure (MD = 2.89; 95% CI: 1.94-3.84; P < 0.001) favoring the control group. The pooled studies were not heterogeneous (I2 = 0%; P = 0.42). As a result, electronic cigarettes had a more substantial negative influence on systolic blood pressure than the control group (Figure 5).

	electron	ic cigare			ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean SD		Total	Mean SD		Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 E-cig With NIcotine									
Antoniewicz 2019 [61]	114.5	12	15	109.4	9.5	15	6.0%	5.10 [-2.65, 12.85]	
Cossio 2020 [7]	120	8	16	119	10	16	7.2%	1.00 [-5.27, 7.27]	
Moheimani 2017 [31]	1.2	2	33	-1.7	2	33	11.2%	2.90 [1.93, 3.87]	
Subtotal (95% CI)			64			64	24.4%	2.89 [1.94, 3.84]	•
leterogeneity: Tau ² = 0.00; Chi	² = 0.66, df	= 2 (P =	0.72); l²	= 0%					
Test for overall effect: Z = 5.98	P < 0.0000	01)							
.2.2 E-cig Without Nicotine									
Antoniewicz 2019 [61]	108.8	15.4	15	109.3	10.3	15	4.9%	-0.50 [-9.88, 8.88]	
Cossio 2020 [7]	121	10	16	115	8	16	7.2%	6.00 [-0.27, 12.27]	
Moheimani 2017 [31]	-0.8	1.9	33	-1.7	2	33	11.2%	0.90 [-0.04, 1.84]	T
Subtotal (95% CI)			64			64	23.3%	1.55 [-1.10, 4.20]	◆
Heterogeneity: Tau ² = 2.11; Chi		= 2 (P =	0.28); l²	= 23%					
Test for overall effect: Z = 1.15 ((P = 0.25)								
1.2.3 Vaping									
Benowitz [38]	120.2	15.3	36	116	15.6	36	6.5%	4.20 [-2.94, 11.34]	
Dimitriadis 2022 phase 1 [37]	127	6	12	113	4	12	9.1%	14.00 [9.92, 18.08]	
Dimitriadis 2022 phase 2 [37]	133	5	12	112	5	12	9.2%	21.00 [17.00, 25.00]	
Sonzalez 2021 [36]	122	4	15	119	4	15	10.1%	3.00 [0.14, 5.86]	
Kerr 2019 [33]	123	11	20	124	12	20	6.5%	-1.00 [-8.13, 6.13]	
Aoheimani 2017 [31]	115.8	2.5	16	109	2.6	18	10.9%	6.80 [5.08, 8.52]	-
Subtotal (95% CI)			111			113	52.3%	8.30 [2.78, 13.83]	
Heterogeneity: Tau ² = 41.91; Ch	ni² = 69.61,	df = 5 (P	< 0.000	01); l ² =	93%				
est for overall effect: Z = 2.94	(P = 0.003)								
Total (95% CI)			239			241	100.0%	5.67 [2.90, 8.43]	◆
leterogeneity: Tau ² = 17.47; Ch	ni² = 146.68	3. df = 11	(P < 0.0	0001):	l ² = 93 ⁴	%			
est for overall effect: Z = 4.02								_	-20 -10 0 10 20
001 101 010101 01100L Z - 4.0Z		df = 2 (P						Fa	vours electronic cigarettes smoking Favours Control

FIGURE 5: Forest plot: mean difference in systolic blood pressure with electronic cigarette smoking.

The pooled analysis of the included studies showed no significant difference between the e-cigarette smokers without nicotine and the control group regarding the MD of the systolic blood pressure (MD = 1.55; 95% CI: -1.10-4.20; P = 0.25). The pooled studies had low heterogeneity (I2 = 23%; P = 0.28). Thus, the effects of nicotine-free vaping on SBP were compared to those of a placebo group

The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers (vaping irrespective of the nicotine content) and the control group regarding the MD of the systolic blood pressure (MD = 8.30; 95% CI: 2.78-13.83; P = 0.003). The pooled studies were highly heterogeneous (I2 = 93%; P < 0.0001). There was a high degree of heterogeneity across the studies, even though vaping was more negatively impactful on SBP than control, regardless of whether or not nicotine was present

The pooled analysis of three groups showed a significant mean difference in the systolic blood pressure with smoking e-cigarettes with and without nicotine and e-cigarette use compared to control groups (MD = 5.67; 95% CI: 2.90-8.43; P < 0.001). The pooled studies were heterogeneous (I2 = 93%; P < 0.0001), and the heterogeneity could not be resolved by leaving one out. The subgroup differences showed moderate heterogeneity (I2 = 57.2%; P= 0.10).

Diastolic Blood Pressure Changes in Individuals Using E-Cigarettes

The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers with nicotine and the control group regarding the mean difference (MD) of the diastolic blood pressure (MD = 3.10; 95% CI: 0.42-5.78; P = 0.02) favoring the control group. The pooled studies were not heterogeneous (I2 = 0%; P = 0.35). As a result, electronic cigarettes had a more substantial negative influence on diastolic blood pressure than the control group (Figure 6).

		ic cigare			rol gro			Mean Difference	Mean Difference
Study or Subgroup	Mean SD		Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.3.1 E-cig With Nicotine									
Antoniewicz 2019 [61]	74.9	5.8	15	70.3	5.7	15	8.7%	4.60 [0.48, 8.72]	
Cossio 2020 [7]	71	6	16	69	4	16	10.0%	2.00 [-1.53, 5.53]	
Subtotal (95% CI)			31			31	18.7%	3.10 [0.42, 5.78]	◆
Heterogeneity: Tau ² = 0.00; Chi		= 1 (P = 1	0.35); I ²	= 0%					
Test for overall effect: Z = 2.27 ((P = 0.02)								
1.3.2 E-cig Without Nicotine									
Antoniewicz 2019 [61]	72.2	8	15	70.2	5.8	15	7.1%	2.00 [-3.00, 7.00]	
Cossio 2020 [7]	70	5	16	66	4	16	10.9%	4.00 [0.86, 7.14]	
Subtotal (95% CI)			31			31	18.0%	3.44 [0.78, 6.09]	◆
Heterogeneity: Tau ² = 0.00; Chi ²	² = 0.44, df	= 1 (P = 1	0.51); I ²	= 0%					
Test for overall effect: Z = 2.53 ((P = 0.01)								
1.3.3 Vaping									
Benowitz [38]	76.7	12.5	36	73.2	11.9	36	6.1%	3.50 [-2.14, 9.14]	+
Dimitriadis 2022 phase 1 [37]	72.4	4	12	66	3	12	11.7%	6.40 [3.57, 9.23]	
Dimitriadis 2022 phase 2 [37]	75	5	12	64	3	12	10.5%	11.00 [7.70, 14.30]	
Gonzalez 2021 [36]	70	2	15	68	2	15	15.1%	2.00 [0.57, 3.43]	-
Kerr 2019 [33]	80	10	20	80	11	20	5.0%	0.00 [-6.52, 6.52]	
Moheimani 2017 [31]	73.5	2.3	16	70	2	18	15.0%	3.50 [2.04, 4.96]	
Subtotal (95% CI)			111			113	63.4%	4.65 [2.05, 7.25]	•
Heterogeneity: Tau ² = 7.48; Chi ²	² = 29.04, d	lf = 5 (P <	0.0001)	; I ² = 83	\$%				
Test for overall effect: Z = 3.51 ((P = 0.0005)							
Total (95% CI)			173			175	100.0%	4.12 [2.37, 5.87]	◆
Heterogeneity: Tau ² = 4.77; Chi	² = 30.55, d	lf = 9 (P =	0.0004	; l ² = 71	%				
est for overall effect: Z = 4.61 (-20 -10 0 10 20
Test for subgroup differences: C			= 0.69)	$l^2 = 0\%$				Favo	ours electronic cigarettes smoking Favours control

FIGURE 6: Forest plot: mean difference in diastolic blood pressure with electronic cigarette smoking.

The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers without nicotine and the control group regarding the MD of the diastolic blood pressure (MD = 3.44; 95% CI: 0.78-6.09; P = 0.01) favoring the control group. The pooled studies were not heterogeneous (I2 = 0%; P = 0.51). Thus, vaping was negatively impactful on diastolic blood pressure even without the presence of nicotine.

The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers (irrespective of the nicotine content) and the control group regarding the MD of the diastolic blood pressure (MD = 4.65; 95% CI: 2.05-7.5; P < 0.0001) favoring the control group. The pooled studies were moderately heterogeneous (I2 = 83%; P < 0.001). Therefore, vaping negatively affected diastolic blood pressure more than the control.

The overall pooled analysis of 4 groups showed a significant MD of the diastolic blood pressure with smoking e-cigarettes with and without nicotine and tobacco and e-cigarette use compared to control groups (MD = 4.12; 95% CI: 2.37-5.87; P < 0.0001). The pooled studies had low heterogeneity (I2 = 71%; P < 0.001). The subgroup differences showed no heterogeneity (I2 = 0%; P= 0.69).

Mean Blood Pressure Changes in Individuals Using E-Cigarettes

The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers and the control group regarding the MD of the mean blood pressure (MD = 7.05; 95% CI: 2.70-1.40; P = 0.001) favoring the control group. The pooled studies were of high heterogeneity (I2 = 94%; P < 0.001) (Figure 7). Accordingly, vaping negatively impacted the MBP more than the control group.

	electroni	Co	ontro	1		Mean Difference	Mean Difference						
Study or Subgroup	Mean SD Tota		Total	Mean SD Total		Weight	IV, Random, 95% C	IV, Random, 95% CI					
Dimitriadis 2022 phase 1 [37]	90	3	12	82	3	12	24.8%	8.00 [5.60, 10.40]	_				
Dimitriadis 2022 phase 2 [37]	94	4	12	80	3	12	24.1%	14.00 [11.17, 16.83]					
Gonzalez 2021 [36]	90	3	15	88	3	15	25.2%	2.00 [-0.15, 4.15]					
Moheimani 2017 [31]	87.6	2.3	16	83	2	18	26.0%	4.60 [3.14, 6.06]					
Total (95% CI)			55			57	100.0%	7.05 [2.70, 11.40]	-				
	Total (95% CI) 55 Heterogeneity: Tau ² = 18.39; Chi ² = 50.14, df = 3 (P < 0.00001); l ² = 94% Test for overall effect: Z = 3.18 (P = 0.001)								-20 -10 0 10 20 avours electronic cigarettes smoking Favours Control				

FIGURE 7: The mean difference of the mean blood pressure with electronic cigarette smoking.

Heart Rate Changes in Individuals Using E-Cigarettes

The pooled analysis of the included studies showed a significant difference between the e-cigarette smokers and the control group regarding the MD of heart failure (MD = 3.13; 95% CI: 0.96-5.29; P = 0.005), favoring the control group. The pooled studies had moderate heterogeneity (I2 = 76%; P = 0.0007). Consequently, vaping was found to have a negative impact on HR compared to the control (Figure 8).

	electronic cigarettes			Cont	rol gro	oup		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Benowitz [63]	68.7	11.8	36	66.8	11.2	36	10.2%	1.90 [-3.41, 7.21]	
Dimitriadis 2022 phase 1 [37]	71	6	12	64	5	12	12.6%	7.00 [2.58, 11.42]	
Dimitriadis 2022 phase 2 [37]	75	8	12	64	5	12	10.2%	11.00 [5.66, 16.34]	
Gonzalez 2021 [36]	75	4	15	75	4	15	18.2%	0.00 [-2.86, 2.86]	
lp 2020 [11]	66.5	3.8	43	63.7	2.2	65	24.5%	2.80 [1.54, 4.06]	
Moheimani 2017 [31]	64	2	16	63	2	18	24.2%	1.00 [-0.35, 2.35]	+-
Total (95% CI)			134			158	100.0%	3.13 [0.96, 5.29]	◆
Heterogeneity: Tau ² = 4.57; Chi ²	= 21.18, d	f = 5 (P =	= 0.0007); l ² = 7	6%				-10 -5 0 5 10
Test for overall effect: Z = 2.83 (P = 0.005)							Fav	-10 -5 0 5 10 ours electronic cigarettes smoking Favours Control

FIGURE 8: Forest plot: mean difference in the heart rate with electronic cigarette smoking.

Qualitative data analysis

Heart Failure in Individuals Using E-cigarettes

In an American study of 484 participants (adults with heart failure), e-cigarettes were used only by 1% of the participants. Only 5% of heart failure participants were dual users because they believed e-cigarettes cause less harm. That is to say e-cigarettes are not safe. Therefore, those at risk of serious outcomes avoid using e-cigarettes. It was recommended to assess and monitor the use of e-cigarettes as a harm-reduction approach [42].

QTc Interval in Individuals Using E-cigarettes

In the United States (US), heart rate variability and corrected QT interval measures were used to screen for secondhand smoke among five otherwise healthy volunteers with no cardiovascular illness history. In a randomized, repeated measures crossover study of healthy nonsmoking volunteers, it was concluded that short-term exposure to secondhand e-cigarettes emissions was associated with a significant reduction in the mean of the standard deviation of normal-to-normal intervals (SDNN), the average of the SDNN (ASDNN) intervals, the root mean square of successive differences (rMSSD), QTc interval, and heart rate. The reduction of the heart rate variability measures and the QTc interval was associated with the nicotine content of the e-cigarettes [43].

ECG indices of ventricular repolarization (Tpeak to Tend(Tp-e), Tp-e/QT, and Tp-e/QTc) were significantly longer in tobacco smokers than e-cigarettes smokers with nicotine, according to the findings of a study carried out in the US on 145 adult participants. These participants included long-term e-cigarette and tobacco product users and individuals who had never smoked tobacco. The adverse impact of tobacco and e-cigarettes on ventricular repolarization was associated with a rise in the risk of sudden death [9].

Discussion

The long-term health consequences of consuming electronic cigarettes are yet unclear. Evidence, however, suggests they may be detrimental to the cardiovascular system [44]. E-cigarettes are meant to appear and feel like conventional cigarettes and are often used by those attempting to quit smoking [45]. Studies have shown that e-cigarettes can increase the risk of MI and heart failure with an increased risk of mortality due to the nicotine content - a highly addictive substance [46]. When individuals start using e-cigarettes, they develop tolerance, requiring progressively higher nicotine levels to experience the same stimulation. This may eventually drive individuals to progressively increase their nicotine dose (by excessive smoking), resulting in addiction and reliance on e-cigarettes, which can raise the risk of serious cardiovascular events [13-47]. In addition, e-cigarettes contain other harmful chemicals, such as metals and chemicals that can damage the lungs [48]. Therefore, switching to e-cigarette smoking confers less risk of MI compared to tobacco smoking. However, those who smoked e-cigarettes had a higher risk of MI than those who had never smoked or had quit smoking. This suggests that vaping may prevent MI compared to traditional tobacco smoking. However, there is still a risk of MI associated with e-cigarette use. On the other hand, the studies carried out were heterogeneous, reflecting the great differences in sampling and design.

The findings of the qualitative review revealed that continuous exposure to e-cigarette emissions with nicotine enhances sympathetic predominance, which was demonstrated by decreased heart rate variability measures and lengthening of the QTc interval, indicating a rise in cardiovascular risk [43]. In addition, it was concluded that e-cigarettes with nicotine, rather than without nicotine, prolong the ECG indexes of ventricular repolarization comparable to tobacco cigarette smoking [9]. Prolonging the ECG indexes of ventricular repolarization reflects the increased susceptibility to ventricular arrhythmias [49] with an increased risk of sudden death [50].

Despite the increasing evidence of increased HF risk with e-cigarette smoking [51], only one study was conducted in the last five years. In this study, e-cigarettes were used by patients with heart failure because of the expected reduced harm to nearby individuals and themselves [42]. It was postulated that the risk of heart

failure is increased by increased risk factors, including arterial blood pressure, heart rate, and atherosclerosis [18-52].

The literature suggests that tobacco and e-cigarettes release nicotine to blood circulation, activating the sympathetic nervous system [46-53]. The nicotine-derived sympathetic activation is emphasized to impact the cardiovascular system causing an increase in blood pressure, heart rate, myocardial contractility, and coronary spasm [54].

In this meta-analysis study, the impact of e-cigarettes, especially nicotine, on the sympathetic activity of the heart was obvious regarding SBP, DBP, MBP, and HR. E-cigarettes significantly elevate systolic blood pressure irrespective of the nicotine content in the e-cigarettes subgroup. On the other hand, the impact of e-cigarettes on diastolic blood pressure was more robust. In addition, e-cigarette use was significantly associated with increased mean blood pressure. In accordance with the increase in sympathetic activity, e-cigarettes were found to increase HR significantly.

The findings of this study match the recent literature. A recent study showed that both heart rates and mean blood pressure increase during vaping, and the MBP do not decrease in recovery, negatively affecting the muscle sympathetic nerve activity [36]. Compared to tobacco cigarette use, e-cigarettes acutely elevate blood pressure and HR, an effect attributable to nicotine rather than non-nicotine use [55]. Therefore, the excitatory effect of e-cigarettes on the heart has been well established [56]. However, recent studies have only focused on contrasting traditional and electronic cigarettes to conclude that the latter has fewer health risks [57]. The current body of evidence on the impacts of electronic cigarettes does not confer being harmless [54-59]. Unless supported by stronger evidence, the electronic cigarette should not be assigned as a cardiovascular-safe product [60-61].

Methodological quality assessment was done on all the included studies (Table 1) using the Hawker Appraisal Tool [29]. All the included studies had a high-quality assessment score of 78-100%. Of the total 15 studies assessed, nine attained a score of 100%, while only one study scored less than 80% with a minimum score of 28. Thus, the studies showed a minimal risk of bias in the overall evidence.

Cureus

	1- Abstract	2-Introduction and	3-Method and	4-	5-Data	6-Ethics and	7-	8-	9-		
Author/year	and title	aims	data	Sampling	analysis	bias	Results	5- Transferability	Implications	scoring	percentage
Alzahrani T et al. (2018) [41]	4	4	4	4	4	4	4	4	4	36	100
Antoniewicz et al. (2019) [61]	3	4	4	3	3	4	3	3	3	30	83
Benowitz et al. (2020) [38]	4	4	4	4	4	4	4	4	4	36	100
Cossio et al. (2020)[7]	2	2	2	3	4	4	3	4	4	28	78
Critcher and Siegel (2021) [40]	4	4	4	4	4	4	4	4	4	36	100
Dimitriadis et al. (2022) [37]	3	4	4	4	4	4	4	4	4	35	97
Gathright et al. (2020) [42]	3	3	4	4	4	4	3	2	3	30	83
Gonzalez and Cooke (2021) [36]	4	4	4	4	4	4	4	4	4	36	100
Hiler et al. (2017)[35]	4	4	4	4	4	4	4	4	4	36	100
Hiler et al. (2020)[34]	4	4	4	4	4	4	4	4	4	36	100
lp et al. (2020) [9]	4	4	4	4	4	4	4	4	4	36	100
Kerr et al. (2019)[33]	4	4	3	4	3	4	3	3	3	31	86
Lee et al. (2019)[43]	4	4	4	4	4	4	4	4	4	36	100
Moheimani et al. (2017) [31]	4	4	4	4	4	4	4	4	4	36	100
Vindhya et al. (2020) [39]	3	3	3	4	4	4	4	4	4	33	92

TABLE 1: Hawker appraisal of the selected papers.

Conclusions

The current systematic review and meta-analysis with qualitative review emphasize the detrimental effects of e-cigarettes on the cardiovascular system. The findings of this review concurred with the previous literature on raising awareness of the risks of e-cigarettes on the heart. E-cigarettes impose a cardio-excitatory effect on the heart with an increased risk of heart failure and coronary insufficiency. There is published evidence that e-cigarettes should not be considered safe and harmless. Therefore, e-cigarettes should not be encouraged in patients with compromised cardiovascular systems.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

- 1. Guo Y, Li S, Wang Z, Jiang F, Guan Y, Huang M, Zhong G: Nicotine delivery and pharmacokinetics of an electronic cigarette compared with conventional cigarettes in Chinese adult smokers: a randomized openlabel crossover clinical study. Nicotine Tob Res. 2022, 24:1881-8. 10.1093/ntr/ntac143
- 2. He K, Chen X, Shi Z, et al.: Relationship of resting heart rate and blood pressure with all-cause and

cardiovascular disease mortality. Public Health. 2022, 208:80-8. 10.1016/j.puhe.2022.03.020

- Middlekauff HR: Cardiovascular impact of electronic-cigarette use. Trends Cardiovasc Med. 2020, 30:133-40. 10.1016/j.tcm.2019.04.006
- Electronic cigarette. (2022). Accessed: March 10, 2022: https://www.cdc.gov/tobacco/basic_information/ecigarettes/index.htm..
- 5. Zhang M, Han C, Wang C, et al.: Association of resting heart rate and cardiovascular disease mortality in hypertensive and normotensive rural Chinese. J Cardiol. 2017, 69:779-84. 10.1016/j.jjcc.2016.07.015
- Watson M, Dardari Z, Kianoush S, et al.: Relation between cigarette smoking and heart failure (from the Multiethnic Study of Atherosclerosis). Am J Cardiol. 2019, 123:1972-7. 10.1016/j.amjcard.2019.03.015
- Cossio R, Cerra ZA, Tanaka H: Vascular effects of a single bout of electronic cigarette use . Clin Exp Pharmacol Physiol. 2020, 47:3-6. 10.1111/1440-1681.13180
- Chatterjee S, Caporale A, Tao JQ, et al.: Acute e-cig inhalation impacts vascular health: a study in smoking naïve subjects. Am J Physiol Heart Circ Physiol. 2021, 320:H144-58. 10.1152/ajpheart.00628.2020
- Ip M, Diamantakos E, Haptonstall K, et al.: Tobacco and electronic cigarettes adversely impact ECG indexes of ventricular repolarization: implication for sudden death risk. Am J Physiol Heart Circ Physiol. 2020, 318:H1176-84. 10.1152/ajpheart.00738.2019
- Liu X, Yuan Z, Ji Y: The association between electronic cigarettes, sleep duration, and the adverse cardiovascular outcomes: Findings from behavioral risk factor surveillance system, 2020. Front Cardiovasc Med. 2022, 9:909383. 10.3389/fcvm.2022.909383
- 11. Alzahrani T, Pena I, Temesgen N, Glantz SA: Association between electronic cigarette use and myocardial infarction. Am J Prev Med. 2018, 55:455-61. 10.1016/j.amepre.2018.05.004
- Rodríguez-Núñez I, Pontes RB, Romero F, Campos RR: Effects of physical exercise on baroreflex sensitivity and renal sympathetic nerve activity in chronic nicotine-treated rats. Can J Physiol Pharmacol. 2021, 99:786-94. 10.1139/cjpp-2020-0381
- Jensen KP, Valentine G, Gueorguieva R, Sofuoglu M: Differential effects of nicotine delivery rate on subjective drug effects, urges to smoke, heart rate and blood pressure in tobacco smokers. Psychopharmacology (Berl). 2020, 237:1359-69. 10.1007/s00213-020-05463-6
- Narkar A, Feaster TK, Casciola M, Blinova K: Human in vitro neurocardiac coculture (ivNCC) assay development for evaluating cardiac contractility modulation. Physiol Rep. 2022, 10:e15498. 10.14814/phy2.15498
- Ramalingam A, Budin SB, Mohd Fauzi N, Ritchie RH, Zainalabidin S: Targeting mitochondrial reactive oxygen species-mediated oxidative stress attenuates nicotine-induced cardiac remodeling and dysfunction. Sci Rep. 2021, 11:13845. 10.1038/s41598-021-93234-4
- Kloner RA: Marijuana and electronic cigarettes on cardiac arrhythmias . Heart Rhythm. 2023, 20:87-8. 10.1016/j.hrthm.2022.09.022
- Richardson A, Krivokhizhina T, Lorkiewicz P, D'Souza S, Bhatnagar A, Srivastava S, Conklin DJ: Effects of electronic cigarette flavorants on human platelet aggregation ex vivo. Toxicol Rep. 2022, 9:814-20. 10.1016/j.toxrep.2022.04.003
- El-Mahdy MA, Ewees MG, Eid MS, Mahgoup EM, Khaleel SA, Zweier JL: Electronic cigarette exposure causes vascular endothelial dysfunction due to NADPH oxidase activation and eNOS uncoupling. Am J Physiol Heart Circ Physiol. 2022, 322:H549-67. 10.1152/ajpheart.00460.2021
- Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. PLoS Med. 2009, 6:e1000097. 10.1371/journal.pmed.1000097
- Thomas KH, Davies NM, Taylor AE, Taylor GM, Gunnell D, Martin RM, Douglas I: Risk of neuropsychiatric and cardiovascular adverse events following treatment with varenicline and nicotine replacement therapy in the UK Clinical Practice Research Datalink: a case-cross-over study. Addiction. 2021, 116:1532-45. 10.1111/add.15338
- Goniewicz ML, Miller CR, Sutanto E, Li D: How effective are electronic cigarettes for reducing respiratory and cardiovascular risk in smokers? A systematic review. Harm Reduct J. 2020, 17:91. 10.1186/s12954-020-00440-w
- Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ. 2003, 327:557-60. 10.1136/bmj.327.7414.557
- Huang J, Wang Y, Duan Z, Kim Y, Emery SL, Chaloupka FJ: Do e-cigarette sales reduce the demand for nicotine replacement therapy (NRT) products in the US? Evidence from the retail sales data. Prev Med. 2021, 145:106376. 10.1016/j.ypmed.2020.106376
- Mersha AG, Gould GS, Bovill M, Eftekhari P: Barriers and facilitators of adherence to nicotine replacement therapy: a systematic review and analysis using the Capability, Opportunity, Motivation, and Behaviour (COM-B) Model. Int J Environ Res Public Health. 2020, 17: 10.3390/ijerph17238895
- Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R: EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. PLoS One. 2013, 8:e66317. 10.1371/journal.pone.0066317
- Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L: Nicotine levels in electronic cigarettes. Nicotine Tob Res. 2013, 15:158-66. 10.1093/ntr/nts103
- 27. Farsalinos KE, Kistler KA, Gillman G, Voudris V: Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. Nicotine Tob Res. 2015, 17:168-74. 10.1093/ntr/ntu176
- Haddaway NR, Page MJ, Pritchard CC, McGuinness LA: PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst Rev. 2022, 18:e1230. 10.1002/cl2.1230
- 29. Hawker S, Payne S, Kerr C, Hardey M, Powell J: Appraising the evidence: reviewing disparate data systematically. Qual Health Res. 2002, 12:1284-99. 10.1177/1049732302238251
- Lin L, Chu H: Quantifying publication bias in meta-analysis. Biometrics. 2018, 74:785-94. 10.1111/biom.12817
- 31. Moheimani RS, Bhetraratana M, Yin F, Peters KM, Gornbein J, Araujo JA, Middlekauff HR: Increased cardiac sympathetic activity and oxidative stress in habitual electronic cigarette users: implications for

cardiovascular risk. JAMA Cardiol. 2017, 2:278-84. 10.1001/jamacardio.2016.5303

- Moheimani RS, Bhetraratana M, Peters KM, et al.: Sympathomimetic effects of acute e-cigarette use: role of nicotine and non-nicotine constituents. J Am Heart Assoc. 2017, 6:10.1161/JAHA.117.006579
- 33. Kerr DM, Brooksbank KJ, Taylor RG, Pinel K, Rios FJ, Touyz RM, Delles C: Acute effects of electronic and tobacco cigarettes on vascular and respiratory function in healthy volunteers: a cross-over study. J Hypertens. 2019, 37:154-66. 10.1097/HJH.000000000001890
- Hiler M, Karaoghlanian N, Talih S, Maloney S, Breland A, Shihadeh A, Eissenberg T: Effects of electronic cigarette heating coil resistance and liquid nicotine concentration on user nicotine delivery, heart rate, subjective effects, puff topography, and liquid consumption. Exp Clin Psychopharmacol. 2020, 28:527-39. 10.1037/pha0000337
- Hiler M, Breland A, Spindle T, et al.: Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: influence of liquid nicotine concentration and user experience. Exp Clin Psychopharmacol. 2017, 25:380-92. 10.1037/pha0000140
- Gonzalez JE, Cooke WH: Acute effects of electronic cigarettes on arterial pressure and peripheral sympathetic activity in young nonsmokers. Am J Physiol Heart Circ Physiol. 2021, 320:H248-55. 10.1152/ajpheart.00448.2020
- Dimitriadis K, Narkiewicz K, Leontsinis I, et al.: Acute effects of electronic and tobacco cigarette smoking on sympathetic nerve activity and blood pressure in humans. Int J Environ Res Public Health. 2022, 19:10.3390/ijerph19063237
- Benowitz NL, St Helen G, Nardone N, et al.: Twenty-four-hour cardiovascular effects of electronic cigarettes compared with cigarette smoking in dual users. J Am Heart Assoc. 2020, 9:e017317. 10.1161/JAHA.120.017317
- Vindhyal MR, Okut H, Ablah E, Ndunda PM, Kallail KJ, Choi WS: Cardiovascular outcomes associated with adult electronic cigarette use. Cureus. 2020, 12:e9618. 10.7759/cureus.9618
- 40. Critcher CR, Siegel M: Re-examining the association between e-cigarette use and myocardial infarction: a cautionary tale. Am J Prev Med. 2021, 61:474-82. 10.1016/j.amepre.2021.05.003
- 41. Alzahrani T, Pena I, Temesgen N, Glantz SA: Association between electronic cigarette use and myocardial infarction. Am J Prev Med. 2018, 55:455-461.
- Gathright EC, Wu WC, Scott-Sheldon LA: Electronic cigarette use among heart failure patients: findings from the Population Assessment of Tobacco and Health study (Wave 1: 2013-2014). Heart Lung. 2020, 49:229-32. 10.1016/j.hrtlng.2019.11.006
- Lee MS, Rees VW, Koutrakis P, Wolfson JM, Son YS, Lawrence J, Christiani DC: Cardiac autonomic effects of secondhand exposure to nicotine from electronic cigarettes: an exploratory study. Environ Epidemiol. 2019, 3:10.1097/EE9.00000000000033
- 44. Sharma A, Gupta I, Venkatesh U, Singh AK, Golamari R, Arya P: E-cigarettes and myocardial infarction: a systematic review and meta-analysis. Int J Cardiol. 2023, 371:65-70. 10.1016/j.ijcard.2022.09.007
- 45. Hartmann-Boyce J, Lindson N, Butler AR, et al.: Electronic cigarettes for smoking cessation . Cochrane Database Syst Rev. 2021, 10.1002/14651858.CD010216.pub6
- Berlowitz JB, Xie W, Harlow AF, et al.: E-cigarette use and risk of cardiovascular disease: a longitudinal analysis of the PATH Study (2013-2019). Circulation. 2022, 145:1557-9. 10.1161/CIRCULATIONAHA.121.057369
- Klonizakis M, Gumber A, McIntosh E, Brose LS: Short-term cardiovascular effects of e-cigarettes in adults making a stop-smoking attempt: a randomized controlled trial. Biology (Basel). 2021, 10:10.3390/biology10111208
- Spoladore R, Daus F, Pezzini S, Milani M, Limonta A, Savonitto S: The point on the electronic cigarette more than 10 years after its introduction. Eur Heart J Suppl. 2022, 24:1148-52. 10.1093/eurheartjsupp/suac105
- Topilski I, Rogowski O, Rosso R, et al.: The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. J Am Coll Cardiol. 2007, 49:320-8. 10.1016/j.jacc.2006.08.058
- Alizade E, Yesin M, Yazicioğlu MV, et al.: Evaluation of Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with asymptomatic arrhythmogenic right ventricular cardiomyopathy. Ann Noninvasive Electrocardiol. 2017, 22:10.1111/anec.12362
- Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, et al.: Cigarette smoking exposure and heart failure risk in older adults: the Health, Aging, and Body Composition study. Am Heart J. 2012, 164:236-42. 10.1016/j.ahj.2012.05.013
- 52. Morales-Oyarvide V, Richards D, Hendren NS, et al.: Hemodynamic gain index and exercise capacity in heart failure with preserved ejection fraction. Am J Cardiol. 2023, 190:17-24. 10.1016/j.amjcard.2022.11.049
- 53. Etter JF: A longitudinal study of cotinine in long-term daily users of e-cigarettes . Drug Alcohol Depend. 2016, 160:218-21. 10.1016/j.drugalcdep.2016.01.003
- Benowitz NL, Burbank AD: Cardiovascular toxicity of nicotine: Implications for electronic cigarette use . Trends Cardiovasc Med. 2016, 26:515-23. 10.1016/j.tcm.2016.03.001
- Arastoo S, Haptonstall KP, Choroomi Y, et al.: Acute and chronic sympathomimetic effects of e-cigarette and tobacco cigarette smoking: role of nicotine and non-nicotine constituents. Am J Physiol Heart Circ Physiol. 2020, 319:H262-70. 10.1152/ajpheart.00192.2020
- 56. Kennedy CD, van Schalkwyk MC, McKee M, Pisinger C: The cardiovascular effects of electronic cigarettes: a systematic review of experimental studies. Prev Med. 2019, 127:105770. 10.1016/j.ypmed.2019.105770
- 57. Garcia PD, Gornbein JA, Middlekauff HR: Cardiovascular autonomic effects of electronic cigarette use: a systematic review. Clin Auton Res. 2020, 30:507-19. 10.1007/s10286-020-00683-4
- MacDonald A, Middlekauff HR: Electronic cigarettes and cardiovascular health: what do we know so far? . Vasc Health Risk Manag. 2019, 15:159-74. 10.2147/VHRM.S175970
- Middlekauff HR: Cardiovascular effects of electronic cigarettes. Nat Rev Cardiol. 2020, 17:379-81. 10.1038/s41569-020-0370-3
- Skotsimara G, Antonopoulos AS, Oikonomou E, et al.: Cardiovascular effects of electronic cigarettes: a systematic review and meta-analysis. Eur J Prev Cardiol. 2019, 26:1219-28. 10.1177/2047487319832975
- 61. Antoniewicz L, Brynedal A, Hedman L, Lundbäck M, Bosson JA: Acute effects of electronic cigarette

inhalation on the vasculature and the conducting airways. Cardiovasc Toxicol. 2019, 19:441-50. 10.1007/s12012-019-09516-x