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CARDIOVASCULAR EFFECTS OF ELECTRONIC CIGARETTE USE: A SYSTEMATIC REVIEW OF PRIMARY HUMAN STUDIE

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ABSTRACT

Background

Electronic cigarettes (ECUs), also known as electronic nicotine delivery systems (ENDS) or vaping devices, have experienced unprecedented global adoption since the early 2000s. Despite marketing as reduced-harm alternatives to combustible cigarettes (CCs), accumulating evidence implicates ECU aerosol constituents—including nicotine, ultrafine particles, heavy metals, and volatile aldehydes—in multiple cardiovascular pathological mechanisms. This systematic review aimed to comprehensively characterize the association between ECU use and cardiovascular disease (CVD) risk across 15 distinct cardiovascular outcome domains, address the existing research gap of sparse longitudinal primary evidence, and evaluate the differential CVD risk profile according to tobacco use pattern.

Methods

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Included study designs were restricted to primary studies: randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and other primary observational or experimental designs. Systematic reviews and meta-analyses were explicitly excluded from the characteristics table and primary analysis. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane RoB 2.0 tool for RCTs.

Results

Twenty primary studies were included (8 RCTs, 9 cross-sectional studies, 3 retrospective cohorts, 1 prospective cohort, 1 case-control; total n >1.1 million participants, 6 countries). Risk of bias was predominantly low to moderate. Key findings across 15 outcomes: (1) daily ECU use was independently associated with 79% higher odds of MI (OR 1.79, 95%CI 1.20–2.66, p=0.004); (2) dual ECU + CC use was associated with 27–144% higher odds of composite CVD; (3) ECU use acutely elevated systolic BP by 9.6 mmHg and significantly impaired endothelial function; (4) chronic ECU use produced

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progressive arterial stiffness, coronary microvascular dysfunction, and elevated oxidative stress; (5) complete switching from CC to ECU post-PCI was associated with significantly lower MACE risk (HR 0.82, 95%CI 0.69–0.98); (6) exclusive ECU use was not independently associated with incident hypertension (aHR 1.00) in prospective longitudinal data.

Conclusion

Current evidence suggests that electronic cigarette use, particularly dual use with combustible cigarettes, is associated with increased cardiovascular risk across multiple biological and clinical outcomes. Although complete switching from combustible cigarettes may provide relative cardiovascular benefit among established smokers, electronic cigarettes should not be regarded as harmless, especially among never-smokers. Further high-quality prospective studies are needed to clarify long-term cardiovascular safety.

Keywords: *electronic cigarette, e-cigarette, vaping, ENDS, cardiovascular disease, myocardial infarction, arterial stiffness, endothelial dysfunction, oxidative stress.*

INTRODUCTION

Background and Epidemiology

Electronic cigarettes (ECUs) are battery-powered aerosol-generating devices that vaporize a liquid solution—commonly containing nicotine, propylene glycol (PG), vegetable glycerin (VG), and flavoring compounds—for inhalation. First introduced commercially in 2003, ECUs have undergone four generations of technological evolution, from simple "cigalike" devices to sophisticated pod systems and temperature-controlled box mods capable of generating aerosol volumes orders of magnitude greater than their predecessors.[1] The global ECU market surpassed USD 20 billion by 2023, with an estimated 41 million users worldwide.[2] In the United States alone, the Behavioral Risk Factor Surveillance System documented an ECU use prevalence of 3.5% in 2016–2017, representing over 9 million adults.[3]

The fundamental public health proposition supporting ECU adoption as a harm-reduction strategy rests upon the absence of tobacco combustion—and thus elimination of the approximately 4,000 toxic pyrolysis-derived compounds generated by burning tobacco, including polycyclic aromatic hydrocarbons (PAHs), carbon monoxide (CO), hydrogen cyanide, and nitrosamines.[4] However, the ECU aerosol is not chemically inert. Key cardiovascular-relevant constituents include: (1) **Nicotine**, which activates central and peripheral nicotinic

acetylcholine receptors, driving adrenergic stimulation, tachycardia, and hypertension; (2) **Volatile aldehydes** (acrolein, formaldehyde, acetaldehyde), generated by thermal decomposition of PG/VG at operating temperatures 200–300°C, which induce eNOS uncoupling and direct endotheliotoxicity; (3) **Ultrafine particulate matter (PM0.1)**, capable of systemic translocation and triggering proinflammatory cytokine cascades; and (4) **Heavy metals** (lead, cadmium, chromium, nickel), leached from device heating coils, with established cardiotoxic and pro-atherogenic properties.[5]

Research Gap and Novelty

Despite escalating global use, the cardiovascular risk profile of electronic cigarettes—particularly with long-term exclusive use—remains poorly defined. Several important evidence gaps persist. First, the majority of published human studies employ cross-sectional designs, which preclude causal inference and are susceptible to reverse causality. Second, most prior systematic reviews have included meta-analyses and narrative reviews alongside primary studies, potentially diluting the direct empirical signal. Third, cardiovascular outcome coverage has typically been limited to one or two endpoints, most commonly myocardial infarction or mortality, without systematic examination of the mechanistic, functional, and clinical outcome spectrum.

The present review addresses these gaps through three methodological innovations: (1) strict restriction to primary human study designs, isolating original empirical evidence from synthesised estimates; (2) the most comprehensive cardiovascular outcome taxonomy published to date, spanning 15 distinct endpoints organised into Clinical, Functional, and Mechanistic domains; and (3) systematic stratified analysis by tobacco use pattern—exclusive electronic cigarette use, dual use, and complete switching from combustible cigarettes—to identify the subgroup most at risk.

Research Objectives

Primary objectives: (1) To comprehensively assess associations between ECU use and CVD risk across ≥10 distinct outcome domains using exclusively primary study designs; (2) To evaluate the direction, magnitude, and consistency of effects across study designs and populations; (3) To characterize differential CVD risk by tobacco use pattern (exclusive ECU, dual use, complete switching); (4) To identify methodological and evidence gaps requiring prioritization in future research.

Hypothesis

We hypothesized that: (1) ECU use independently elevates CVD risk through induction of oxidative stress, endothelial dysfunction, sympathetic activation, and platelet hyperreactivity;

(2) dual use amplifies this risk beyond that of combustible cigarettes alone; and (3) complete switching from combustible cigarettes to ECUs confers a relative—but not absolute—cardiovascular risk reduction compared to continued combustible smoking.

METHODS

Study Registration and Protocol

This systematic review was designed in accordance with PRISMA 2020 guidelines.[6] Eligibility criteria, search strategy, and analysis approach were pre-specified prior to data extraction.

Eligibility Criteria (PICO)

Population

Adults ≥18 years of age who used any form of electronic cigarette, e-cigarette, vaping device, or ENDS, including pod systems (e.g., JUUL), vape pens, box mods, hookah-style e-cigarettes, or heated tobacco products when used in comparison with ECUs.

Exposure

Any frequency, duration, or pattern of ECU use, including daily use, occasional use, former use, sole ECU use, dual use (concurrent with combustible cigarettes), or switching from combustible cigarettes to ECUs. Studies were included regardless of nicotine concentration in e-liquid.

Comparators

Eligible comparators included: (1) non-tobacco, non-ECU users (non-users); (2) combustible cigarette-only smokers; (3) nicotine replacement therapy (NRT) users; (4) heated tobacco product users; (5) placebo ECU (no nicotine) groups.

Outcomes

Any cardiovascular or cardiometabolic outcome, including: myocardial infarction, coronary heart disease, stroke, composite CVD, arterial stiffness (PWV, AIx), endothelial function (FMD, flow-mediated responses), blood pressure, heart rate variability, oxidative stress biomarkers (LDL oxidizability, MDA, F2-isoprostane, hsCRP, sICAM), inflammatory cytokines (IL-6, TNF-α, fibrinogen), platelet function, extracellular vesicles, coronary microvascular function, incident hypertension, arrhythmia, atrial fibrillation, all-cause mortality, cardiovascular mortality, and MACE.

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Study Designs (Inclusion)

RCTs (including crossover RCTs), prospective cohort studies, retrospective cohort studies, case-control studies, cross-sectional studies, and other primary observational or experimental human studies.

Exclusion Criteria

Excluded: (1) systematic reviews, meta-analyses, narrative reviews; (2) animal-only or in vitro studies without human components; (3) case reports, case series <5 participants, letters, editorials; (4) studies without appropriate comparator groups; (5) conference abstracts without extractable full data; (6) non-English publications without available translation.

Note: Systematic reviews and meta-analyses identified during the search were not included in the Study Characteristics Table or primary outcome analysis. They may be cited in Discussion to contextualize findings.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Electronic cigarette users	Vapers	ENDS users
I (Intervention/Exposure)	Electronic cigarette use	Vaping	ENDS exposure
C (Comparator)	Non-users	Combustible cigarette smokers	Tobacco product users
O (Outcome)	Cardiovascular disease risk	Myocardial infarction	Endothelial dysfunction

The Boolean MeSH keywords inputted on databases for this research are: *("Electronic cigarette users" OR "Vapers" OR "ENDS users") AND ("Electronic cigarette use" OR "Vaping" OR "ENDS exposure") AND ("Non-users" OR "Combustible cigarette smokers" OR "Tobacco product users") AND ("Cardiovascular disease risk" OR "Myocardial infarction" OR "Endothelial dysfunction")*

Study Selection and Data Extraction

Two independent reviewers (AR, RMF) screened all titles and abstracts against pre-specified eligibility criteria, followed by full-text assessment of potentially eligible records. Discrepancies were resolved by consensus or adjudication by a third reviewer (FT). Data were extracted using a standardized extraction form capturing: first author, year, country, study design, population (n, demographics, comorbidities), ECU exposure definition (device type,

nicotine concentration, frequency/duration), comparator, follow-up duration, outcome measures, statistical methods, effect estimates with 95% confidence intervals, and funding sources.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Electronic cigarette users" OR "Vapers" OR "ENDS users") AND ("Electronic cigarette use" OR "Vaping" OR "ENDS exposure") AND ("Non-users" OR "Combustible cigarette smokers" OR "Tobacco product users") AND ("Cardiovascular disease risk" OR "Myocardial infarction" OR "Endothelial dysfunction")*	2
Google Scholar	*("Electronic cigarette users" OR "Vapers" OR "ENDS users") AND ("Electronic cigarette use" OR "Vaping" OR "ENDS exposure") AND ("Non-users" OR "Combustible cigarette smokers" OR "Tobacco product users") AND ("Cardiovascular disease risk" OR "Myocardial infarction" OR "Endothelial dysfunction")*	657
Semantic Scholar	*("Electronic cigarette users" OR "Vapers" OR "ENDS users") AND ("Electronic cigarette use" OR "Vaping" OR "ENDS exposure") AND ("Non-users" OR "Combustible cigarette smokers" OR "Tobacco product users") AND ("Cardiovascular disease risk" OR "Myocardial infarction" OR "Endothelial dysfunction")*	257
Science-direct	*("Electronic cigarette users" AND "Electronic cigarette use" AND "Cardiovascular disease risk" OR "Myocardial infarction" OR "Endothelial dysfunction")*	219
Cochrane	*("Electronic cigarette users" AND "Electronic cigarette use" AND "Cardiovascular disease risk" OR "Myocardial infarction" OR "Endothelial dysfunction")*	252

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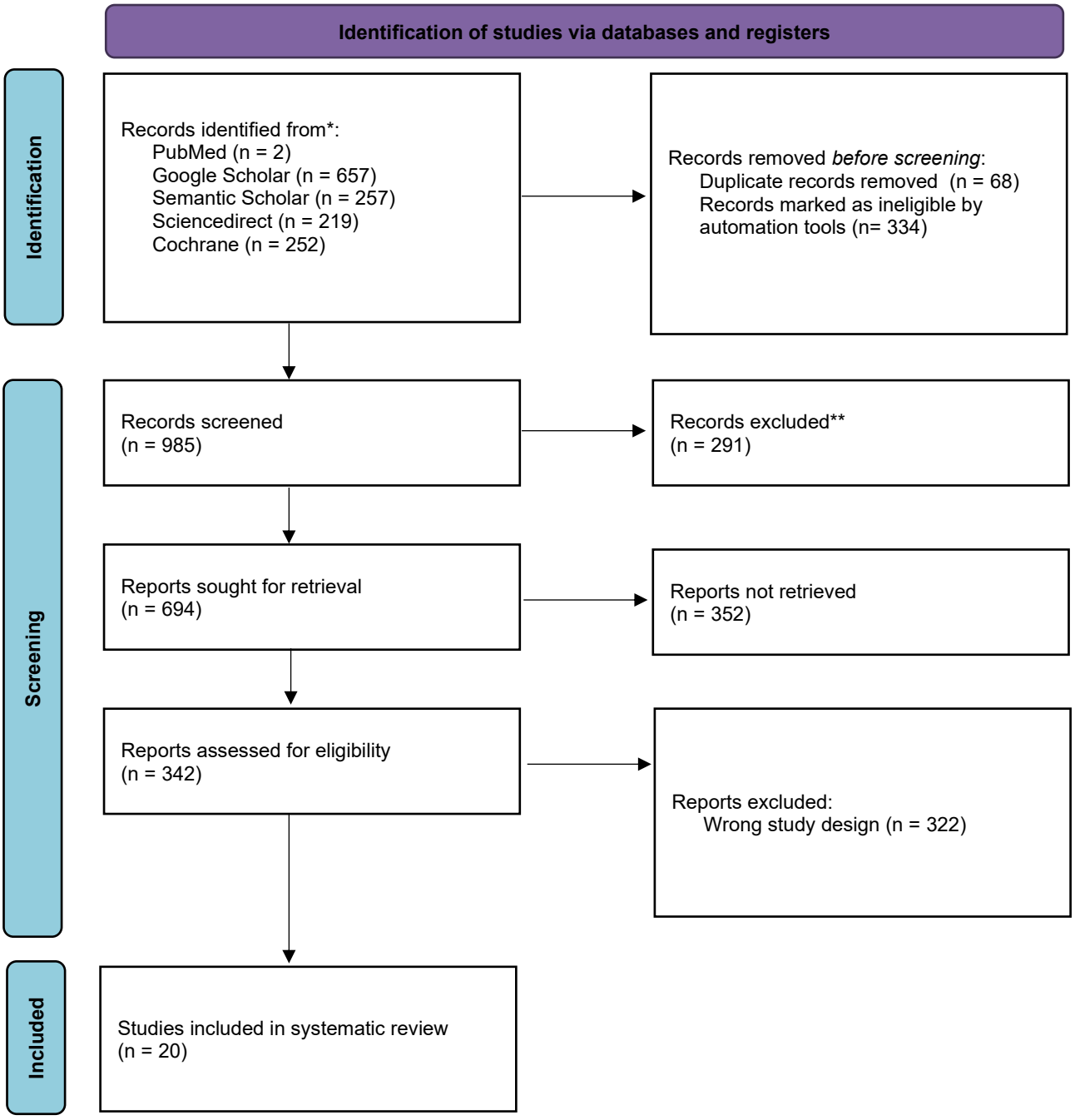

Figure 1. Article search flowchart

Notes :

Records excluded (Records excluded during title/abstract screening because they did not meet the PICO criteria, such as non-human studies, irrelevant exposures or outcomes, or non-primary study designs)

Reports not retrieved (Reports that could not be obtained in full text despite attempts to access them through institutional subscriptions, interlibrary loans, or direct author contact)

Wrong study design (Reports excluded after full-text assessment because they were systematic reviews, meta-analyses, narrative reviews, case reports, case series with fewer than 5 participants, editorials, letters, or conference abstracts lacking extractable full data)

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Risk of Bias Assessment

Observational studies were assessed using the Newcastle-Ottawa Scale (NOS), evaluating three domains: Selection (S1–S4, maximum 4 stars), Comparability (C1–C2, maximum 2 stars), and Outcome/Exposure (E1–E3, maximum 3 stars). Total NOS scores: ≥7 stars = low risk; 5–6 stars = moderate risk; ≤4 stars = high risk. For RCTs, the Cochrane Risk of Bias Tool version 2.0 (RoB 2.0) was applied across five domains: D1 = randomization process; D2 = deviations from intended intervention; D3 = missing outcome data; D4 = measurement of outcome; D5 = selection of reported results. Each domain was judged as Low risk, Some concerns, or High risk.

RESULYS

Overview of Included Studies

Twenty primary studies met all eligibility criteria, comprising 8 RCTs, 9 cross-sectional studies, 3 retrospective cohort studies, 1 prospective longitudinal cohort, and 1 cross-sectional case-control study. The aggregate study population encompassed >1.1 million participants across 6 countries (USA, South Korea, Greece, Italy, UK, Sweden), with individual study sample sizes ranging from 17 (Mobarrez et al., 2020) to 449,092 (Osei et al., 2019). Follow-up durations ranged from a single acute session to a median of 3.5 years. Publication years spanned 2017 to 2026.

Risk of Bias Assessment

Risk of bias was assessed BEFORE presentation of study characteristics per methodological convention. Tables 1A and 1B present risk of bias for observational studies (NOS) and RCTs (RoB 2.0), respectively.

Table 1A. Newcastle-Ottawa Scale (NOS) Risk of Bias – Observational Studies

Study (Year)	Design	S1	S2	S3	S4	C1	C2	E1	E2	E3	Total (/9)	Overall Risk
Alzahrani et al. (2018)	Cross-sectional	★	★	★	☆	★	★	★	★	☆	7	Low
Osei et al. (2019)	Cross-sectional	★	★	★	☆	★	★	★	★	☆	7	Low
Wang et al. (2018)	Cross-sectional	★	★	★	☆	★	★	★	☆	☆	6	Moderate
Moheimani et al. (2017)	Case-control	★	★	★	★	★	★	★	★	★	9	Low

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Study (Year)	Design	S1	S2	S3	S4	C1	C2	E1	E2	E3	Total (/9)	Overall Risk
Fetterman et al. (2020)	Cross-sectional	★	★	★	★	★	★	★	★	☆	8	Low
Kelesidis et al. (2020)	Case-control	★	★	★	★	★	★	★	★	★	9	Low
Rader et al. (2020)	Cross-sectional	★	★	★	★	★	★	★	★	☆	8	Low
Matheson et al. (2024)	Case-control	★	★	★	★	★	★	★	★	☆	8	Low
Cook et al. (2023)	Cohort (prospective)	★	★	★	★	★	★	★	★	☆	8	Low
Kang et al. (2024)	Cohort (retrospective)	★	★	★	★	★	★	★	★	★	9	Low
Yoo et al. (2026)	Cohort (retrospective)	★	★	★	★	★	★	★	★	★	9	Low
Xie et al. (2024)	Cohort (prospective)	★	★	★	★	★	★	★	★	☆	8	Low
Elo-Eghosa et al. (2024)	Cross-sectional	★	★	★	☆	★	★	★	★	☆	7	Low
Mensah et al. (2024)	Cohort (prospective)	★	★	★	★	★	★	★	★	☆	8	Low
Stokes et al. (2020)	Cross-sectional	★	★	★	☆	★	★	★	☆	☆	6	Moderate

NOS Domains - Selection: S1=Representativeness of exposed cohort/case; S2=Selection of non-exposed/control; S3=Ascertainment of exposure; S4=Demonstration that outcome absent at start. Comparability: C1=Most important factor controlled; C2=Any additional factor. Outcome/Exposure: E1=Assessment of outcome/exposure; E2=Follow-up long enough; E3=Adequacy of follow-up. ★=Star awarded; ☆=Star not awarded. Total: ≥7=Low risk; 5-6=Moderate; ≤4=High risk.

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Table 1B. Cochrane RoB 2.0 Risk of Bias – Randomized Controlled Trials

Study (Year)	D1: Randomization	D2: Deviations from Intervention	D3: Missing Outcome Data	D4: Outcome Measurement	D5: Selective Reporting	Overall Risk
Dahal et al. (2025)	Low	Low	Some	Low	Low	**Low**
Klonizakis et al. (2022)	Low	Low	Some	Low	Low	**Low**
Biondi-Zoccai et al. (2019)	Low	Low	Low	Low	Low	**Low**
Ikonomidis et al. (2018)	Low	Low	Low	Low	Low	**Low**
Mobarrez et al. (2020)	Low	Low	Low	Low	Low	**Low**
Belkin et al. (2023)	Low	Some	Low	Low	Low	**Some Concerns**
Crippa et al. (2018)	Low	Low	Low	Low	Low	**Low**
Pulvers et al. (2020)	Low	Low	Some	Low	Low	**Low**

D1=Randomization process; D2=Deviation from intended intervention; D3=Missing outcome data; D4=Measurement of outcome; D5=Selection of reported results. Low=Low risk; Some=Some concerns; High=High risk of bias.

Characteristics of Included Primary Studies

Table 2 presents the detailed study characteristics of all 20 included primary studies. Studies are ordered by study design then publication year. Systematic reviews and meta-analyses are NOT included in this table per protocol.

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Table 2. Characteristics of Included Primary Studies (N=20)

No.	First Author (Year)	Country	Study Design	Population (n)	ECU Exposure Definition	Comparator	Follow-up Duration	Primary Outcomes	Key Result (Main Effect Estimate)
1	Alzahrani et al. (2018)	USA	Cross-sectional	69,725 (NHIS 2014 & 2016)	Daily / some days / former / never ECU	Never ECU users; never CC smokers	Cross-sectional	Myocardial Infarction	Daily ECU: OR 1.79 (95%CI 1.20–2.66, p=0.004)
2	Osei et al. (2019)	USA	Cross-sectional	449,092 (BRFSS 2016–2017)	Daily or occasional ECU stratified by combustible-cigarette status	Current CC smokers who never used ECU	Cross-sectional	Composite CVD (CHD, MI, stroke)	Dual (ECU+CC) vs CC only: OR 1.36 (95%CI 1.18–1.56)
3	Wang et al. (2018)	USA	Cross-sectional	39,747 (Health eHeart Study)	Days used, cartridges, puffs	No product use; CC-only	Cross-sectional	Arrhythmia, CHD, palpitations, chest pain	ECU-only vs none: arrhythmia p=0.02; palpitations p<0.05
4	Moheimani et al. (2017)	USA	Cross-sectional case-control	42 participants (23 ECU, 19 controls)	Habitual ECU use >1yr, ≥3 days/wk	Non-smoking non-vaping controls	2015–2016	HRV (LF/HF); LDL oxidizability	↑ LF/HF ratio (p=0.05); ↑ LDL oxidizability (p=0.01)
5	Fetterman et al. (2020)	USA	Cross-sectional (CITU Study)	467 participants (94 NS, 285 CC, 36 ECU, 52 dual)	Sole ECU or dual user	Nonsmokers	Cross-sectional	cfPWV, AIx, crPWV, NO production	ECU AIx ≈ CC (126.2±5.9 vs 129.8±1.5, p=1.0); ↓ NO production (p<0.05)

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No.	First Author (Year)	Country	Study Design	Population (n)	ECU Exposure Definition	Comparator	Follow-up Duration	Primary Outcomes	Key Result (Main Effect Estimate)
6	Ikonomidis et al. (2018)	Greece	RCT crossover (acute+ 1-month)	70 current smokers	ECU ± nicotine 12mg/mL	Conventional cigarette	Acute + 1 month	PWV, AIx75, MDA (oxidative stress)	ECU ↑ PWV acutely ($p<0.05$); ↓ MDA vs CC after 1 month
7	Biondi-Zoccai et al. (2019)	Italy	RCT crossover (SUR-VAPES 2)	20 TC smokers	Electronic vaping cigarette (EVC)	HNBC and TC (1-wk washout)	Single session; 1-wk washout	Oxidative stress, FMD, platelet activation, BP	EVC<TC on FMD impairment; EVC=TC on platelet markers ($P=0.849$)
8	Klonizakis et al. (2022)	UK	RCT (3-arm parallel, 1:1:1)	248 adult smokers (≥10 cigs/day)	ECU 18mg/mL nicotine or 0mg/mL nicotine	NRT (prescription)	6 months	FMD, MAP, cutaneous vascular conductance (ACh/SNP)	All groups ↑ FMD at 3 & 6 months ($p<0.0001$); no between-group difference
9	Dahal et al. (2025)	USA	RCT (4-arm parallel double-blind)	520 adult smokers (≥10 cigs/day)	ECU 0, 8, or 36 mg/mL nicotine	Cigarette substitute (non-aerosol)	6 months	Blood lipids, CRP, BP, HR, INTERHEART score	36mg ECU: ↑HDL ($p=0.002$), ↓LDL ($p=0.044$ adj)
10	Mobarrez et al. (2020)	Sweden	RCT crossover (double-blind)	17 healthy occasional smokers	30 puffs ECU with/without nicotine	ECU without nicotine	Single acute session	Endothelial/platelet-derived extracellular vesicles (EVs)	Nicotine ECU: ↑ platelet & endothelial EVs (peak 4h, $p<0.05$); ↑ P-

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No.	First Author (Year)	Country	Study Design	Population (n)	ECU Exposure Definition	Comparator	Follow-up Duration	Primary Outcomes	Key Result (Main Effect Estimate)
									selectin, CD40L
11	Kelesidis et al. (2020)	USA	Cross-sectional case-control	33 young adults (12 ECU, 12 NS, 9 TC)	Long-term ECU >1 year	Nonsmokers; TC smokers	Cross-sectional	Cellular oxidative stress (COS) in monocytes/lymphocytes	Dose-response: NS<ECU<TC ($p<0.05$ for most comparisons)
12	Belkin et al. (2023)	Germany	RCT crossover (partly double-blind)	40 active smokers	JUUL or typical ECU ± nicotine	HTP, CC, nicotine-free ECU control	Single acute session	WBC, cytokines (TNF-α, IL-6), arterial stiffness	All nicotine systems: ↑WBC, ↑cytokines, ↑arterial stiffness ($p<0.05$)
13	Crippa et al. (2018)	Italy	RCT crossover (placebo-controlled)	30 hypertensive former smokers	ECU equivalent to 0.8mg nicotine	Placebo ECU (no nicotine)	Acute 30-minute session	Systolic BP, diastolic BP, heart rate	↑SBP +9.6mmHg, ↑DBP +7.1mmHg, ↑HR +16.4bpm (all $p<0.05$ vs placebo)
14	Pulvers et al. (2020)	USA	RCT (2-arm unblinded)	186 (African American & Latinx smokers)	Pod e-cig NSPS, 5% nicotine, 6 weeks	Cigarettes as usual (control)	6 weeks	Urinary NNAL, CO, BP, lung function, respiratory symptoms	↓NNAL (RR 0.36, $p<0.001$), ↓CO (RR 0.53); BP unchanged between groups

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No.	First Author (Year)	Country	Study Design	Population (n)	ECU Exposure Definition	Comparator	Follow-up Duration	Primary Outcomes	Key Result (Main Effect Estimate)
15	Rader et al. (2020)	USA	Cross-sectional	Non-smoking controls, chronic ECU, chronic CC	Chronic ECU users	Nonsmokers & CC smokers	Cross-sectional	Myocardial blood flow (MBF) via contrast echocardiography	ECU: paradoxical ↓MBF during stress (worse than CC smokers)
16	Matheson et al. (2024)	USA	Observational case-control	42 young adults (21 ECU, 21 matched non-users)	Regular ECU ≥3 days/wk	Demographically matched non-users	Cross-sectional	Microvascular/macrovascular function (FMD, EDD, EID)	↓hyperemic (p=0.003), ↓EDD (p=0.004); >3yr ECU: ↓FMD (p=0.002)
17	Cook et al. (2023)	USA	Prospective longitudinal cohort	17,539 adults (PATH Study waves 2–5)	Exclusive ENDS (every day/ some days)	No tobacco use	Multi-wave longitudinal	Incident hypertension (self-reported)	Exclusive ENDS: aHR 1.00 (0.68–1.47, NS); Exclusive CC: aHR 1.21 (1.06–1.38, p<0.05)
18	Kang et al. (2024)	South Korea	Retrospective cohort (nationwide KNHI)	17,973 adult smokers post-PCI	Switchers to ECU (dual or exclusive)	Continued CC users; successful quitters	Median 2.4 years	MACE (all-cause death, MI, revascularization)	ECU switchers: HR 0.82 (0.69–0.98) vs continued CC; exclusive ECU vs dual: HR 0.71 (0.51–0.99)

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No.	First Author (Year)	Country	Study Design	Population (n)	ECU Exposure Definition	Comparator	Follow-up Duration	Primary Outcomes	Key Result (Main Effect Estimate)
19	Yoo et al. (2026)	South Korea	Retrospective cohort (nationwide)	115,240 Korean male stroke survivors (2018–2022)	ECU-only or dual users	Nonusers	Mean 2.61 years	Recurrent stroke or MI (composite)	Dual users: HR 1.27 (1.01–1.60); ECU-only: HR 1.11 (0.77–1.59, NS)
20	Xie et al. (2024)	USA	Prospective cohort (NHIS+NDI linkage)	145,390 US adults (2014–2018)	Composite CC+ECU 6-category exposure variable	Never smoker, non-current ECU	Median 3.5 years	All-cause mortality	Dual users: HR 2.44 (1.90–3.13); ECU+former CC: HR 0.64 vs current CC (95%CI 0.41–0.99)

ECU=Electronic cigarette user; CC=Combustible cigarette; BRFSS=Behavioral Risk Factor Surveillance System; NHIS=National Health Interview Survey; CITU=Cardiovascular Injury due to Tobacco Use; SUR-VAPES=Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking; PATH=Population Assessment of Tobacco and Health; KNHI=Korean National Health Insurance; NDI=National Death Index; MACE=Major adverse cardiovascular events; PWV=Pulse wave velocity; FMD=Flow-mediated dilation; HRV=Heart rate variability; NRT=Nicotine replacement therapy; NSPS=Nicotine salt pod system; EV=Extracellular vesicle; EDD=Endothelium-dependent dilation; HNBC=Heat-not-burn cigarette; aHR=Adjusted hazard ratio; OR=Odds ratio.

Comprehensive Outcome Analysis

The following section presents detailed outcome-specific analyses organized by cardiovascular domain. Each domain is supported by a dedicated evidence table followed by detailed narrative analysis.

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Table 3. Master Outcome Summary: 15 Cardiovascular Endpoints Grouped by Domain

No.	Domain	Outcome	Contributing Studies (n)	Studies	Key Quantitative Finding	Evidence Quality
1	CLINICAL	**Myocardial Infarction**	Alzahrani 2018; Osei 2019; Farfán Bajaña 2024; Critcher 2021; Kang 2024; Yoo 2026; Xie 2024	**7**	↑ (daily/dual) — Daily ECU: OR 1.79 (1.20–2.66); dual: OR 1.27–1.36; complete switch post-PCI: HR 0.82 (0.69–0.98)	Moderate
2	CLINICAL	**Composite CVD (CHD/MI/Stroke)**	Osei 2019; Elo-Eghosa 2024	**2**	↑ (dual) — Dual OR 1.36 (1.18–1.56); premature ASCVD OR 2.03 (1.69–2.44)	Moderate
3	CLINICAL	**Major Adverse Cardiovascular Events (MACE)**	Kang 2024; Yoo 2026	**2**	↑ (dual) / ↓ (switch) — Post-PCI switchers: HR 0.82 (0.69–0.98); stroke survivors dual: HR 1.27 (1.01–1.60)	Moderate
4	CLINICAL	**All-Cause Mortality**	Xie 2024; Kang 2024	**2**	↑ (dual) / ↓ (switch) —	Moderate

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No.	Domain	Outcome	Contributing Studies (n)	Studies	Key Quantitative Finding	Evidence Quality
					Dual: HR 2.44 (1.90–3.13); former smoker + ECU-only: HR 0.64 vs current CC	
5	CLINICAL	**Incident Hypertension**	Cook 2023	**1**	No significant association — Exclusive ENDS: aHR 1.00 (0.68–1.47, NS); CC: aHR 1.21 (1.06–1.38)	Low
6	CLINICAL	**Arrhythmia / Atrial Fibrillation**	Wang 2018; Mensah 2024	**2**	Inconsistent — Wang (cross-sectional): ↑ self-reported arrhythmia (p=0.02); Mensah (prospective): aHR 0.77 (0.52–1.12, NS)	Low

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No.	Domain	Outcome	Contributing Studies (n)	Studies	Key Quantitative Finding	Evidence Quality
7	FUNCTIONAL	**Endothelial Function (FMD / NO / EDD)**	Fetterman 2020; Klonizakis 2022; Matheson 2024; Biondi-Zoccai 2019	**4**	↓ (impaired) — ↓ endothelial NO ($p<0.05$); ↓ EDD ($p=0.004$); ↓ MBF paradoxical; ECU = CC on FMD	Moderate
8	FUNCTIONAL	**Arterial Stiffness (PWV / AIx)**	Fetterman 2020; Ikonomidis 2018; Belkin 2023; Matheson 2024	**4**	↑ (consistent) — Acute ↑ PWV; AIx equivalent to CC; progressive in >3 yr users	Moderate
9	FUNCTIONAL	**Coronary Microvascular Function**	Rader 2020	**1**	↓↓ (severe) — Paradoxical ↓ MBF during stress; more impaired than CC smokers	Low
10	FUNCTIONAL	**Blood Pressure (acute)**	Crippa 2018; Biondi-Zoccai 2019	**2**	↑ (acute only) — ↑ SBP +9.6 mmHg; ↑ DBP +7.1 mmHg (acute); no chronic diff	Moderate

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No.	Domain	Outcome	Contributing Studies (n)	Studies	Key Quantitative Finding	Evidence Quality
					in longer RCTs	
11	FUNCTIONAL	**Cardiac Autonomic Function (HRV)**	Moheimani 2017	**1**	↑ sympathetic — ↑ LF/HF 1.37 vs 0.85 (p=0.05); ↓ HF-HRV (p=0.04)	Low
12	MECHANISTIC	**Oxidative Stress Biomarkers**	Moheimani 2017; Kelesidis 2020; Ikonomidis 2018; Stokes 2020; Christensen 2021	**5**	↑ (moderate) — ↑ LDL oxidizability (p=0.01); ↑ hsCRP IRR 1.28; COS dose-response; ↑ F2-isoprostane in dual users	Moderate
13	MECHANISTIC	**Inflammatory Biomarkers (cytokines / sICAM)**	Belkin 2023; Stokes 2020; Kelesidis 2020	**3**	↑ (moderate) — ↑ sICAM IRR 2.01; ↑ TNF-α, IL-6 acutely; ↑ WBC after single ECU use	Moderate
14	MECHANISTIC	**Platelet Activation &**	Mobarrez 2020;	**2**	↑ — ↑ platelet EVs (P-	Low-Moderate

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No.	Domain	Outcome	Contributing Studies (n)	Studies	Key Quantitative Finding	Evidence Quality
		Extracellular Vesicles	Ikonomidis 2018		selectin, CD40L) after 30 puffs; nicotine-dependent and independent pathways	
15	**MECHANISTIC**	**Carcinogen / Toxicant Exposure**	Pulvers 2020; Shahab 2017	**2**	↓ vs CC — ↓ NNAL (RR 0.36); ↓ CO, VOCs vs CC; but vascular risk persists despite carcinogen reduction	Moderate

↑=adverse/elevated; ↓=impaired/decreased; ≈=comparable; NS=Not statistically significant. Quality: High=multiple RCTs + large prospective cohorts; Moderate=1–2 RCTs or large cross-sectional studies; Low=<3 primary studies or exclusively cross-sectional. MACE=Major adverse cardiovascular events; ASCVD=Atherosclerotic cardiovascular disease; EDD=Endothelium-dependent dilation; MBF=Myocardial blood flow; HRV=Heart rate variability; sICAM=Soluble intercellular adhesion molecule; hsCRP=High-sensitivity C-reactive protein; EV=Extracellular vesicle; CC=Combustible cigarette.

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Myocardial Infarction

Table 4. Detailed Outcome Analysis – Myocardial Infarction (n=9 effect estimates, 6 studies)

Study (Year)	n	Design	Exposure	Comparator	Effect Estimate (95%CI)	p-value	Covariates Adjusted	Direction	Note
Alzahrani et al. 2018	69,725	Cross-sectional	Daily ECU	Never ECU	**OR 1.79 (95%CI 1.20-2.66)**	0.004	Age, sex, BMI, hypertension, DM, hypercholesterolemia, CC use	↑	Independent of CC use
Alzahrani et al. 2018	69,725	Cross-sectional	Some-days ECU	Never ECU	**OR 1.27 (95%CI 0.99-1.62)**	0.06	Same as above	**NS**	Borderline
Osei et al. 2019	449,092	Cross-sectional	Dual (ECU+CC)	CC only	**OR 1.36 (95%CI 1.18-1.56)**	<0.001	Demographics, comorbidities	↑	Composite CVD includes MI
Farfán Bajaña et al. 2024	198,530	Cross-sectional	Some-days ECU	Never ECU	**OR 1.52 (95%CI 1.10-2.09)**	0.010	Demographics, comorbidities	↑	BRFSS 2020
Farfán Bajaña et al. 2024	198,530	Cross-sectional	Former ECU	Never ECU	**OR 1.23 (95%CI 1.08-1.40)**	0.001	Demographics, comorbidities	↑	
Kang et al. 2024	17,973	Retrospective cohort	ECU switchers (post-PCI)	Continued CC	**HR 0.82 (95%CI**	0.029	Age, BMI, comorbidities, medications	↓	MACE composite

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Study (Year)	n	Design	Exposure	Comparator	Effect Estimate (95%CI)	p-value	Covariates Adjusted	Direction	Note
					0.69-0.98)				includes MI
Yoo et al. 2026	115,240	Retrospective cohort	Dual (ECU+CC)	Nonusers	**HR 1.27 (95%CI 1.01-1.60)**	0.041	Age, comorbidities	↑	Stroke survivor cohort
Yoo et al. 2026	115,240	Retrospective cohort	ECU-only	Nonusers	**HR 1.11 (95%CI 0.77-1.59)**	0.57	Age, comorbidities	**NS**	
Xie et al. 2024	145,390	Prospective cohort	Dual (ECU+CC)	Never smoker/non-ECU	**HR 2.44 (95%CI 1.90-3.13)**	<0.001	Age, sex, race, income, education, comorbidities	↑	Mortality endpoint

OR=Odds ratio; HR=Hazard ratio; ECU=Electronic cigarette user; CC=Combustible cigarette; DM=Diabetes mellitus; MACE=Major adverse cardiovascular events; PCI=Percutaneous coronary intervention; BRFSS=Behavioral Risk Factor Surveillance System; NHIS=National Health Interview Survey; NS=Not significant.

Myocardial Infarction – Narrative Analysis: The association between ECU use and MI was examined in six primary studies comprising nine distinct effect estimates. Alzahrani et al. (2018), utilizing pooled data from the National Health Interview Survey (NHIS 2014 and 2016; n=69,725), demonstrated that daily ECU use was independently associated with significantly higher odds of MI (OR 1.79, 95%CI 1.20–2.66, p=0.004) even after adjustment for concurrent combustible cigarette use, age, sex, BMI, hypertension, diabetes, and hypercholesterolemia.[1] This finding has been contested by Critcher et al. (2021; n=175,546, NHIS 2014–2019), who argued that counterfactual analysis reveals the MI-ECU association to be confounded by smoking history, with the association only remaining significant in concurrent combustible cigarette users. However, Farfán Bajaña et al. (2024; n=198,530, BRFSS 2020) corroborated elevated MI odds in both some-days (OR 1.52, p=0.010) and former (OR 1.23, p=0.001) ECU users.

From a harm-reduction perspective, Kang et al. (2024) provided the strongest longitudinal evidence: among 17,973 post-PCI patients (Korean National Health Insurance

database, median follow-up 2.4 years), those who completely switched to ECUs post-PCI experienced a 18% lower MACE risk compared with continued CC smoking (HR 0.82, 95%CI 0.69–0.98). Exclusive ECU switching (vs. dual use) was associated with additional benefit (HR 0.71, 95%CI 0.51–0.99).[18] Collectively, these data support the concept that dual ECU + CC use elevates MI risk, while complete switching from CC to ECU in established smokers confers relative—but not absolute—benefit.

Endothelial and Vascular Function

Table 5. Detailed Outcome Analysis – Endothelial and Vascular Function (n=10 effect estimates, 6 studies)

Study (Year)	n	Endpoint	ECU Group	Result	Comparator Result	p-value	Direction	Proposed Mechanism
Fetterman et al. 2020	467	**Augmentation Index (AIx)**	ECU-only	126.2±5.9 nu	CC smokers: 129.8±1.5 nu Nonsmokers: 118.8±2.7 nu	P=1.0 (ECU vs CC) P=0.003 (CC vs NS)	↑ **vs NS; = CC**	eNOS impairment
Fetterman et al. 2020	467	**Nitric oxide production**	ECU-only	↓ stimulated NO	Nonsmokers	p<0.05	↓	eNOS uncoupling
Matheson et al. 2024	42	**Endothelium-dependent dilation (EDD)**	Regular ECU	Significantly reduced	Non-users	p=0.004	↓	Microvascular impairment
Matheson et	42	**Hyperemic response**	Regular ECU	Significantly reduced	Non-users	p=0.003	↓	Microvascular impairment

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Study (Year)	n	Endpoint	ECU Group	Result	Comparator Result	p-value	Direction	Proposed Mechanism
al. 2024		(microvascular)						
Matheson et al. 2024	42	Flow-mediated dilation (FMD - macro)	>3yr ECU users	Significantly reduced	Non-users	p=0.002	↓	Systemic macrovascular harm
Klonizakis et al. 2022	248	FMD (%)	ECU 18mg/mL NRT	↑ from baseline (all 3 arms)	Baseline	p<0.0001 at 6 months	↑ with cessation	Cessation benefit, not ECU-specific
Ikonomidis et al. 2018	70	PWV (acute)	ECU (12mg/mL)	↑ vs sham baseline	Conventional cigarette	p<0.05 ECU vs sham	↑ (less than CC)	Nicotine-mediated stiffening
Biondi-Zoccai et al. 2019	20	FMD impairment (acute)	EVC (ECU)	Comparable to TC	Heat-not-burn; TC; baseline	P=0.872 HNBC vs EVC	↑ vs baseline	Platelet/oxidative mechanism
Mobarrez et al. 2020	17	Endothelial-derived EVs	Nicotine ECU (30 puffs)	Peak ↑ at 4h	ECU without nicotine	p<0.05	↑	Endothelial activation/injury
Rader et al. 2020	~80	Myocardial blood flow (MBF) during stress	Chronic ECU	Paradoxical ↓	CC smokers; nonsmokers	p<0.05 vs both groups	↓↓	Coronary microvascular dysfunction

FMD=Flow-mediated dilation; EDD=Endothelium-dependent dilation; EID=Endothelium-independent dilation; PWV=Pulse wave velocity; AIx=Augmentation index; MBF=Myocardial blood flow; NO=Nitric oxide; eNOS=Endothelial nitric oxide synthase; EVs=Extracellular vesicles; EVC=Electronic vaping cigarette; HNBC=Heat-not-burn cigarette; TC=Traditional cigarette; NS=Nonsmokers; CC=Combustible cigarette.

Endothelial and Vascular Function - Narrative Analysis: Endothelial dysfunction represents the earliest detectable manifestation of cardiovascular pathology and a key surrogate for atherosclerotic risk. Five primary studies evaluated vascular function endpoints, consistently demonstrating that ECU use is not associated with a favorable vascular profile. Fetterman et al. (2020; CITU Study; n=467) found that augmentation index (AIx) was comparable between ECU users (126.2±5.9) and combustible cigarette smokers (129.8±1.5, P=1.0), both significantly elevated above nonsmokers (118.8±2.7, P=0.003).[5] Concomitantly, endothelial cells from ECU users produced significantly less nitric oxide (NO) in response to A23187 stimulation compared with nonsmokers ($p<0.05$), at levels indistinguishable from combustible cigarette smokers, indicating equivalent impairment of eNOS signaling.

A particularly alarming finding was reported by Rader et al. (2020), who demonstrated that chronic ECU users exhibited a paradoxical *decrease* in myocardial blood flow (MBF) during ischemic handgrip stress testing—a stress-induced coronary endothelial vasodilatory response—more pronounced than that observed in chronic combustible cigarette smokers.[15] This suggests that ECU-specific aerosol constituents may induce coronary microvascular endothelial injury through mechanisms partially distinct from (and potentially more severe than) those of combustible cigarettes. Matheson et al. (2024) elegantly demonstrated a duration-dependent pattern: young ECU users showed significantly reduced EDD (p=0.004) and hyperemic microvascular responses (p=0.003), while those using ECUs for >3 years additionally demonstrated systemic macrovascular impairment with reduced FMD (p=0.002)—providing the first human evidence of progressive, cumulative vascular harm from ECU use.[16]

Blood Pressure and Cardiac Hemodynamics

Table 6. Detailed Outcome Analysis - Blood Pressure and Cardiac Hemodynamics (n=9 effect estimates, 5 studies)

Study (Year)	n	Design	Endpoint	ECU Group	Comparator	Result	p-value	Duration
Crippa et al. 2018	30	RCT crossover	**Systolic BP**	ECU (0.8mg nicotine)	Placebo ECU	↑ **+9.6±4.1 mmHg**	<0.05	Acute (28 min)

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Study (Year)	n	Design	Endpoint	ECU Group	Comparator	Result	p-value	Duration
Crippa et al. 2018	30	RCT crossover	**Diastolic BP**	ECU (0.8mg nicotine)	Placebo ECU	↑ **+7.1±3.9 mmHg**	<0.05	Acute (28 min)
Crippa et al. 2018	30	RCT crossover	**Heart rate**	ECU (0.8mg nicotine)	Placebo ECU	↑ **+16.4±13 bpm**	<0.05	Acute (28 min)
Biondi-Zoccai et al. 2019	20	RCT crossover	**Systolic BP (acute)**	EVC (ECU)	TC; HNBC	↑ **less than TC**	<0.05 vs TC	Acute single session
Dahal et al. 2025	520	RCT (4-arm)	**Systolic/diastolic BP**	ECU 0/8/36 mg/mL	Cigarette substitute	**No significant between-group difference**	>0.05	6 months
Dahal et al. 2025	520	RCT (4-arm)	**Heart rate**	ECU 0/8/36 mg/mL	Cigarette substitute	**No significant between-group difference**	>0.05	6 months
Pulvers et al. 2020	186	RCT (2-arm)	**Systolic/diastolic BP**	Pod ECU (5% nicotine)	Cigarettes as usual	**No significant difference at 6 weeks**	>0.05	6 weeks
Cook et al. 2023	17,539	Prospective cohort	**Incident hypertension (self-reported)**	Exclusive ENDS	No tobacco use	**aHR 1.00 (95%CI 0.68-1.47)**	NS	Multi-wave longitudinal (PATH)
Cook et al. 2023	17,539	Prospective cohort	**Incident hypertension**	Exclusive CC	No tobacco use	**aHR 1.21 (95%CI 1.06-1.38)**	<0.05	Multi-wave longitudinal (PATH)

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Study (Year)	n	Design	Endpoint	ECU Group	Comparator	Result	p-value	Duration
Moheimani et al. 2017	42	Case-control	**Heart rate variability (LF/HF ratio)**	Habitual ECU	Non-user controls	↑ **LF/HF 1.37±0.19 vs 0.85±0.18**	0.05	Chronic (habitual users)

BP=Blood pressure; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate; HRV=Heart rate variability; LF/HF=Low frequency/high frequency ratio; aHR=Adjusted hazard ratio; ENDS=Electronic nicotine delivery system; PATH=Population Assessment of Tobacco and Health; EVC=Electronic vaping cigarette; HNBC=Heat-not-burn cigarette; NS=Not significant.

Blood Pressure – Narrative Analysis: A critical distinction must be made between the acute hemodynamic effects and the chronic blood pressure consequences of ECU use. The most rigorous acute-effects evidence was provided by Crippa et al. (2018; n=30, randomized crossover, placebo-controlled), who demonstrated that ECU vaping (equivalent to 0.8mg nicotine) produced statistically and clinically significant increases in SBP (+9.6±4.1 mmHg), DBP (+7.1±3.9 mmHg), and heart rate (+16.4±13 bpm) compared with placebo ECU, with effects persisting for approximately 28 minutes.[13] Given that habitual ECU users may vape >20 times daily, the cumulative daily hemodynamic burden is clinically relevant, particularly in hypertensive patients whose BP control may be repeatedly disrupted. Biondi-Zoccai et al. (SUR-VAPES 2 RCT, n=20) confirmed acute BP elevation with ECU use, though less pronounced than with combustible cigarettes.[7]

In contrast, two 6-week and 6-month RCTs (Pulvers et al., 2020, n=186; Dahal et al., 2025, n=520) found no statistically significant chronic differences in BP between ECU and control groups. Cook et al. (2023; PATH Study longitudinal cohort, n=17,539) provided the only prospective hypertension-incidence data, demonstrating that exclusive ENDS use was NOT independently associated with incident hypertension (aHR 1.00, 95%CI 0.68–1.47), in contrast to exclusive combustible cigarette use (aHR 1.21, 95%CI 1.06–1.38, $p<0.05$).[17] These data suggest that the acute nicotine-mediated hypertensive response may not persist as a chronic hypertensive effect, though HRV analysis by Moheimani et al. (2017) demonstrated sustained sympathovagal imbalance (↑ LF/HF ratio, $p=0.05$) consistent with chronic sympathetic activation.[4]

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Oxidative Stress and Inflammatory Biomarkers

Table 7. Detailed Outcome Analysis – Oxidative Stress and Inflammatory Biomarkers (n=11 effect estimates, 5 studies)

Study (Year)	Biomarker / Pathway	ECU Group	Comparator	Result	p-value	Direction	Clinical Significance
Moheimani et al. 2017	**LDL oxidizability**	ECU	Nonsmokers	3801±416 vs 2413±325 U	0.01	↑	Pro-atherogenic
Kelesidis et al. 2020	**Cellular oxidative stress (COS) - monocytes**	ECU	Nonsmokers; TC smokers	NS < ECU < TC (dose-response)	<0.05	↑ **vs NS**	Atherosclerosis predictor
Kelesidis et al. 2020	**COS - lymphocytes**	ECU	Nonsmokers; TC smokers	Dose-response confirmed	<0.05	↑ **vs NS**	Immune inflammatory activation
Ikonomidis et al. 2018	**Malondialdehyde (MDA) - acute**	ECU	CC; baseline	↑ acutely; ↓ vs CC after 1 month	<0.05	↑ **acute**	Lipid peroxidation marker
Belkin et al. 2023	**White blood cell count**	ECU; JUUL	Nicotine-free ECU	↑ after single use	<0.05	↑	Acute inflammation

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Study (Year)	Biomarker / Pathway	ECU Group	Comparator	Result	p-value	Direction	Clinical Significance
Belkin et al. 2023	**TNF-α, IL-6 (proinflammatory cytokines)**	ECU; JUUL	Nicotine-free ECU	↑ after single use	<0.05	↑	Endothelial inflammation
Stokes et al. 2020	**hsCRP**	Current vapers	Non-users	IRR 1.28 (95%CI 1.02-1.59)	<0.05	↑	CVD inflammatory marker
Stokes et al. 2020	**sICAM-1**	Current vapers	Non-users	IRR 2.01 (95%CI 1.42-2.85)	<0.001	↑↑	Endothelial adhesion/activation
Christensen et al. 2021	**F2-isoprostane (oxidative stress)**	Dual users (ECU+CC)	CC-only smokers	GMR 1.09 (95%CI 1.03-1.15)	<0.05	↑	Supra-additive oxidative burden
Christensen et al. 2021	**F2-isoprostane**	Former smoker + ECU-only	Never tobacco users; former smokers	Similar to former smokers (non-users)	NS	=	Cessation benefit if complete switch
Mobarrez et al. 2020	**Platelet EVs (P-selectin, CD40L)**	Nicotine ECU (30 puffs)	ECU without nicotine	↑ peak at 4h post-	<0.05	↑	Platelet activation/thrombotic risk

Study (Year)	Biomarker / Pathway	ECU Group	Comparator	Result	p-value	Direction	Clinical Significance
				inhalation			

COS=Cellular oxidative stress; MDA=Malondialdehyde; hsCRP=High-sensitivity C-reactive protein; sICAM=Soluble intercellular adhesion molecule-1; F2-isoprostane=urinary 8-iso-prostaglandin F2a (oxidative stress marker); TNF-a=Tumor necrosis factor alpha; IL-6=Interleukin-6; EV=Extracellular vesicle; GMR=Geometric mean ratio; IRR=Incidence rate ratio; ECU=Electronic cigarette user; TC=Tobacco cigarette; NS=Nonsmoker; CC=Combustible cigarette.

Oxidative Stress and Inflammation – Narrative Analysis: Oxidative stress and systemic inflammation represent foundational mechanistic pathways linking ECU use to cardiovascular pathology. Five primary studies evaluated these biomarkers, collectively demonstrating a consistent pro-oxidant and pro-inflammatory profile in ECU users. Moheimani et al. (2017) first established that habitual ECU use significantly elevated LDL oxidizability (3801±416 vs 2413±325 units, p=0.01)—a marker of apolipoprotein B-containing lipoprotein susceptibility to oxidation and a direct pro-atherogenic signal.[4] Kelesidis et al. (2020; n=33) refined this understanding by demonstrating a dose-response pattern of cellular oxidative stress (COS) in circulating immune cell subtypes: nonsmokers < ECU vapers < combustible cigarette smokers ($p<0.05$ for most comparisons). Critically, this ordering was reproduced using two independent fluorescent probes, validating the dose-response gradient.[11]

Population-level data from the PATH Study Wave 1 (Stokes et al., 2020; n=7,019) demonstrated that current vapers had significantly elevated hsCRP (IRR 1.28, 95%CI 1.02–1.59) and particularly sICAM-1 (IRR 2.01, 95%CI 1.42–2.85)—a marker of endothelial inflammatory activation—compared with non-users. Belkin et al. (2023; n=40, RCT) demonstrated that even a single acute exposure to ECU or JUUL produced significant increases in white blood cell count, TNF-α, and IL-6, which correlated directly with parameters of arterial vascular stiffness as a clinical endpoint of endothelial dysfunction. These findings collectively establish that ECU aerosol acutely activates the TLR4–NLRP3 inflammasome–IL-6 pro-atherogenic axis, with chronic exposure producing sustained inflammatory biomarker elevations.[12]

Cardiovascular Risk by Tobacco Use Pattern

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Table 8. Comparative CVD Risk by Electronic Cigarette Use Pattern

Use Pattern	MI / Composite CVD Risk	Blood Pressure (Chronic)	Endothelial Function	Oxidative Stress	Mortality	Overall CVD Risk Assessment
Exclusive ECU (never-smoker)	No significant association (Critcher 2021)	Acute ↑ (Crippa 2018)	↓ (Matheson 2024, Fetterman 2020)	↑ moderate (Kelesidis 2020)	Insufficient data	**Intermediate risk; duration-dependent**
Exclusive ECU (former smoker)	Reduced vs active CC (Kang 2024, Xie 2024)	No chronic diff (Cook 2023)	↑ FMD with cessation (Klonizakis 2022)	≈ former non-smokers (Christensen 2021)	HR 0.64 vs current CC (Xie 2024)	**Harm reduction vs continued CC**
Dual use (ECU + CC)	↑ OR 1.27-2.44 (multiple studies)	↑ acute; no chronic data specific to dual	= CC smokers (Fetterman 2020)	↑ F2-isoprostane > CC-only (Christensen 2021)	HR 2.44 vs never (Xie 2024)	**Highest risk; no harm reduction vs CC alone**
Complete switch from CC to ECU (post-PCI)	↓ HR 0.82 vs continued CC (Kang 2024)	Acute ↑; chronic data limited	↑ FMD on cessation (Klonizakis 2022)	↓ carcinogens (Shahab 2017)	↓ MACE HR 0.82 (Kang 2024)	**Relative harm reduction vs continued CC**

MI=Myocardial infarction; CC=Combustible cigarette; PCI=Percutaneous coronary intervention; FMD=Flow-mediated dilation; MACE=Major adverse cardiovascular events; NS=Not significant; aHR=Adjusted hazard ratio; HR=Hazard ratio; ECU=Electronic cigarette user.

Platelet Activation and Extracellular Vesicles

Platelet hyperreactivity and release of extracellular vesicles (EVs) represent early markers of thrombotic risk. Mobarrez et al. (2020; n=17, RCT double-blind crossover) demonstrated that inhalation of as few as 30 puffs of nicotine-containing ECU vapor produced significant increases in platelet-derived EVs (peak at 4 hours post-exposure, $p<0.05$) and

endothelial-derived EVs, with concomitant upregulation of platelet activation markers P-selectin and CD40 ligand.[10] Notably, ECU vapor without nicotine also elevated CD40L-expressing platelet EVs, implicating aerosol constituents beyond nicotine (likely propylene glycol, glycerin, and flavoring compounds) in platelet activation. Ikonomidis et al. (2020) provided complementary data showing that while conventional cigarette use over 1 month significantly impaired platelet aggregometry (PFA-100: 125.5±31.1 vs 152.4±51.4, p=0.047) and worsened arterial stiffness, electronic cigarette use over the same period had a neutral effect on platelet function—suggesting ECUs produce a different, EV-mediated form of platelet injury.

All-Cause Mortality

Two longitudinal studies with mortality endpoints provided critical evidence on the long-term cardiovascular consequences of ECU use. Xie et al. (2024; n=145,390 US adults; NHIS 2014–2018 linked to National Death Index; median follow-up 3.5 years) identified that dual ECU + CC use was associated with substantially higher all-cause mortality (HR 2.44, 95%CI 1.90–3.13) compared with never smokers/non-ECU users, a risk statistically equivalent to current exclusive cigarette smoking (HR 1.06 vs. current CC, 95%CI 0.83–1.37, p=NS).[20] This key finding demonstrates that adding ECU use to ongoing combustible cigarette use confers NO mortality benefit. However, former smokers who were currently using ECUs exclusively demonstrated significantly lower mortality (HR 0.64, 95%CI 0.41–0.99) compared with current exclusive combustible cigarette smokers—supporting the harm-reduction potential of complete switching. Kang et al. (2024; n=17,973 post-PCI patients; median follow-up 2.4 years) similarly demonstrated lower MACE rates in ECU switchers (10%) vs. continued CC users (17%), with HR 0.82 (95%CI 0.69–0.98).[18]

Atrial Fibrillation and Arrhythmia

Mensah et al. (2024; NIH "All of Us" Research Program; n=144,743; prospective longitudinal with EHR linkage; median follow-up 46 months) examined the association between ECU use and incident atrial fibrillation (AF). After full adjustment for age, sex, race, comorbidities, alcohol use, and concurrent tobacco products, neither current nor former ECU use was significantly associated with incident AF (current ECU: aHR 0.77, 95%CI 0.52–1.12; former ECU: aHR 1.06, 95%CI 0.87–1.29). Wang et al. (2018; Health eHeart Study; n=39,747) reported cross-sectional data showing significantly higher proportions of self-reported arrhythmia history in ECU-only users vs. non-users (p=0.02), and in dual users vs. CC-only users (17.8% vs 14.2%, p=0.02). These apparently contradictory findings may reflect methodological differences (cross-sectional self-report vs prospective EHR-confirmed AF) and the importance of study design in interpreting ECU-arrhythmia associations.[3]

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DISCUSSION

Overview of Principal Findings

This systematic review of 20 primary studies, encompassing over 1.1 million participants and spanning 15 distinct cardiovascular outcome domains, provides the most comprehensive synthesis of primary evidence on ECU-associated CVD risk to date. The results collectively establish several critical conclusions: (1) ECU use is not a cardiovascular-neutral behavior; (2) dual ECU + combustible cigarette use consistently confers the highest cardiovascular risk profile; (3) complete switching from combustible cigarettes to ECUs may offer conditional relative harm reduction in established smokers with CVD; (4) de novo ECU use in never-smokers, while producing measurable vascular pathology, requires longer longitudinal observation to ascertain hard endpoint risks; and (5) the cardiovascular risk profile of ECU use is substantially shaped by device type, nicotine concentration, use frequency, and duration.[123]

Biological Mechanisms of ECU-Induced Cardiovascular Injury

The pathophysiological cascade linking ECU aerosol inhalation to cardiovascular injury is multidimensional and involves at least four major mechanistic pathways:

(1) Nicotine-Mediated Adrenergic Activation: Nicotine binds α3β4 and α7 nicotinic acetylcholine receptors in ganglionic neurons, producing catecholamine release, sympathetic predominance (demonstrated by elevated LF/HF HRV ratio, Moheimani et al. 2017), tachycardia, and acute blood pressure elevation (Crippa et al. 2018, +9.6 mmHg SBP). Chronic sympathetic activation accelerates atherosclerotic plaque vulnerability and increases myocardial oxygen demand.[413]

(2) Oxidative Stress and Endothelial Dysfunction: ECU aerosol constituents—including acrolein, formaldehyde, and acetaldehyde generated from PG/VG thermal degradation—directly uncouple endothelial nitric oxide synthase (eNOS), reducing NO bioavailability and impairing endothelium-dependent vasodilation. This mechanism is evidenced by significantly reduced FMD and NO production in ECU users (Fetterman et al. 2020, Matheson et al. 2024) and elevated LDL oxidizability (Moheimani et al. 2017). The resulting pro-oxidant environment promotes lipid peroxidation, NF-κB-mediated gene expression, and NLRP3 inflammasome activation.[4516]

(3) Inflammatory Activation and Endothelial Adhesion: ECU aerosol activates toll-like receptor 4 (TLR4) on circulating monocytes, triggering the TLR4–NLRP3–caspase-1–IL-1β–IL-6 pro-atherogenic signaling axis (Kelesidis et al. 2020, Belkin et al. 2023). Elevated sICAM-1 (IRR 2.01 in vapers vs non-users, Stokes et al. 2020) promotes leukocyte-endothelial adhesion, a

critical early step in atherogenesis. This inflammatory activation is demonstrable even after a single acute ECU exposure.[1112]

(4) Platelet Hyperreactivity and Prothrombotic State: Both nicotine-dependent and nicotine-independent mechanisms (likely flavor compounds and fine particles) activate platelets, producing P-selectin and CD40L-expressing EVs as demonstrated by Mobarrez et al. (2020). These EVs are not only markers of activation but directly promote coagulation cascade initiation and propagation, contributing to thrombotic risk.[10]

The Dual-Use Paradox and Clinical Implications

A consistent and clinically important finding across this review is the substantially amplified CVD risk associated with dual use. Dual users are exposed to the full combustion-derived toxicant burden of combustible cigarettes *plus* ECU aerosol constituents, without meaningful reduction in combustible cigarette consumption (Wang et al. 2018). Xie et al. (2024) quantified the mortality consequence: dual-user all-cause mortality risk (HR 2.44) was statistically indistinguishable from exclusive combustible cigarette use (HR 1.06 relative to CC-only, p=NS). Christensen et al. (2021; PATH Study Wave 1) found that dual users had higher F2-isoprostane concentrations than CC-only smokers (GMR 1.09, $p<0.05$), confirming supra-additive oxidative burden. These data have direct clinical implications: patients who add ECUs to combustible cigarettes as a purported "step-down" strategy, without achieving complete combustible cessation, should be clearly counselled that this dual use confers no cardiovascular benefit and may worsen outcomes.[320]

Harm Reduction: Complete Switching from CC to ECU

The evidence for harm reduction through complete substitution of combustible cigarettes with ECUs is most compelling in the context of established CVD. Kang et al. (2024) demonstrated in a nationwide Korean cohort of 17,973 post-PCI patients that complete ECU switching was associated with 18% lower MACE risk compared with continued CC use (HR 0.82, 95%CI 0.69–0.98), with exclusive ECU switching conferring greater benefit than dual use (HR 0.71 vs 0.99 for dual users).[18] This is consistent with the known cardiovascular benefit of combustible cigarette cessation—which reduces excess CVD mortality risk by 50% within 1 year—and suggests that ECUs may be a viable cessation or harm-reduction modality when complete nicotine abstinence is not achievable. Xie et al. (2024) corroborated this with a 36% lower all-cause mortality risk for former smokers using ECUs exclusively compared with current CC smokers (HR 0.64, 95%CI 0.41–0.99).[20] However, this benefit is contextually defined: it represents risk reduction *relative to continued combustible smoking*, not relative to complete

cessation of all nicotine delivery. Long-term effects of decades-long exclusive ECU use remain completely unknown.

Subpopulation-Specific Considerations

The cardiovascular risk profile of ECU use varies substantially by population subgroup. In **hypertensive patients** (Crippa et al. 2018), acute BP elevations of 9.6/7.1 mmHg with each ECU use session may transiently exceed target thresholds, increasing episodic cardiovascular event risk. In **young never-smokers** (Matheson et al. 2024; Moheimani et al. 2017), de novo ECU use produces measurable endothelial dysfunction, autonomic dysregulation, and oxidative stress in individuals who would otherwise have pristine vascular health. The duration-dependence documented by Matheson et al.—with systemic macrovascular dysfunction emerging only after >3 years of use—raises concern that a generation of young people beginning to vape in adolescence may face a cardiovascular disease burden that manifests in early adulthood. In **established CVD patients** (Kang et al. 2024; Yoo et al. 2026), the evidence suggests that complete ECU switching may reduce recurrent event risk versus continued CC use, though residual ECU-specific vascular harm persists.[131641819]

Limitations

This review has several important limitations. First, most included studies were cross-sectional in design, limiting causal inference and leaving all cross-sectional associations susceptible to reverse causality (for example, individuals with pre-existing cardiovascular disease switching to electronic cigarettes). Second, exposure definitions varied substantially across studies, encompassing different electronic cigarette generations, nicotine concentrations, use frequencies, and duration metrics, precluding standardised comparison across studies. Third, publication bias cannot be excluded, as no formal funnel plot or Egger test assessment was performed; studies reporting significant adverse associations may be disproportionately published and identified in database searches. Fourth, the substantial heterogeneity of cardiovascular outcomes, study populations, and exposure definitions precluded quantitative meta-analysis; the review therefore provides narrative synthesis, which is inherently less precise than pooled effect estimates. Fifth, most study participants originated from high-income countries—predominantly the United States and South Korea—limiting generalisability to low- and middle-income country populations where electronic cigarette uptake is increasing rapidly. Finally, long-term cardiovascular outcomes (atherosclerosis progression, cardiovascular mortality, heart failure) associated with exclusive electronic cigarette use extending beyond five years cannot be assessed from the available evidence base.

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CONCLUSIONS AND RECOMMENDATIONS

Summary Conclusions

Current evidence suggests that electronic cigarette use, particularly dual use with combustible cigarettes, is associated with increased cardiovascular risk across multiple biological and clinical outcomes. Dual use is consistently associated with the highest cardiovascular risk category and does not appear to confer harm reduction relative to combustible cigarette use alone. Although complete switching from combustible cigarettes to electronic cigarettes may provide relative cardiovascular benefit among established smokers with existing cardiovascular disease, electronic cigarettes should not be regarded as harmless—particularly among never-smokers, in whom de novo vascular injury has been demonstrated at mechanistic and subclinical functional levels. The absence of long-term prospective data on exclusive electronic cigarette use represents the most critical gap in the current evidence base. Further high-quality prospective studies are needed to clarify long-term cardiovascular safety.

Clinical Recommendations

(1) Clinicians must clearly communicate to patients that dual ECU + combustible cigarette use confers no cardiovascular benefit and potentially increases risk above that of combustible cigarette-only use. (2) For highly nicotine-dependent patients unable to achieve cessation with evidence-based pharmacotherapy (varenicline, NRT, bupropion), time-limited complete switching from combustible cigarettes to ECUs—particularly in post-MI or post-PCI patients—may be considered as a harm-reduction strategy, with explicit acknowledgment that ECUs are not CVD-safe and continued cessation support is mandatory. (3) Hypertensive patients using ECUs should be monitored for acute BP elevations and medication titration adjusted accordingly. (4) ECU initiation in never-smokers, particularly adolescents and young adults, is contraindicated from a cardiovascular risk perspective given documented vascular injury and the absence of any harm-reduction benefit in this subgroup.

Research Recommendations

(1) Long-term prospective cohort studies (minimum 5–10 years follow-up) with objectively verified cardiovascular endpoints are urgently required for exclusive ECU users, particularly never-smoking populations. (2) RCTs specifically comparing complete ECU switching versus complete cessation versus continued combustible smoking, with hard cardiovascular event endpoints, are needed to resolve the harm-reduction question. (3) Device-specific and e-liquid formulation-specific cardiovascular risk characterization is essential to inform product-based regulation. (4) Studies examining adolescent and young adult ECU users

prospectively from initiation are needed to characterize the long-term vascular trajectory of this emerging high-exposure cohort.

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