

Coffee and cardiac arrhythmias: Up-date review of the literature and clinical studies

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Abstract

Coffee, next to water, is the most consumed drink in the world. Coffee contains over 1000 chemical compounds, the most popular of which are caffeine, chlorogenic acid, kahweol, cafestol and trigonelline. Numerous studies have shown the beneficial effects of coffee on the cardiovascular system, nervous system, digestive system and kidneys. Due to the high incidence of cardiac arrhythmias, especially atrial fibrillation, the influence of coffee consumption on arrhythmogenesis remains a controversial and clinically important issue. Many mechanisms by which coffee can increase and decrease the risk of arrhythmias have been described. Habitual consumption of moderate amounts of coffee seems to lead to less arrhythmias, which is reflected in the results of many clinical trials and meta-analyses. This review summarizes the mechanisms of coffee action on the heart muscle and the results of the most recent important clinical trials assessing the impact of coffee consumption on the risk of various cardiac arrhythmias. (Cardiol J 2023; 30, 4: 654–667)

Key words: coffee, heart arrhythmia, atrial arrhythmia, ventricular arrhythmia

Introduction

Coffee is the most consumed drink next to water and tea. According to the National Coffee Association United States of America (USA), about 2.25 billion cups are drunk worldwide every day [1]. Data of the International Coffee Organization (ICO) indicate that inhabitants of the Netherlands consume the most coffee — on average of approximately 8.3 kg *per capita*/year (data from 2020). In 2020/2021, around 166.63 million 60-kilogram bags of coffee were consumed worldwide, a slight increase from 164 million bags in the previous year. According to data from the British Coffee Associa-

tion, 95 million cups of coffee are consumed daily in the United Kingdom (UK). In Poland, coffee consumption calculated *per capita*, is about 3.65 kg/year (on average, 1–2 cups of coffee *per capita*/day). In last 10 years of coffee consumption in Poland significantly increased by as much as over 80% [2].

The large popularity of coffee consumption in the world has led to many studies assessing its impact on human health, for example, the effects of coffee consumption on blood pressure and the risk of hypertension [3]. Another review summarizes the influence of coffee consumption on the risk of various diseases including nervous, digestive, cardiovascular and kidney disorders [4, 5].

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Regular and moderate coffee consumption seems to reduce the risk of cardiovascular- and all-cause mortality [6, 7].

The prevalence of cardiac arrhythmias, especially atrial fibrillation (AF), is high worldwide and continues to increase. In 2007, the prevalence of AF cases globally was 28,533 million, while in 2017 it was 37,574 million, and the prevalence of AF in 2050 will be over 60 million cases worldwide [8]. AF significantly increases the risk of death, cardiovascular complications, and also worsens the prognosis in patients with coronavirus disease (COVID-19) [9–11], with increasing healthcare costs [12]. Moreover, arrhythmias have been associated with psychological morbidity, including the risk of depression [13].

An important contributor to cardiac arrhythmias, including AF, is played by modifiable risk factors such as smoking, alcohol abuse, lack of physical activity and sedentary lifestyle, arterial hypertension, obesity, and inappropriate nutritional behavior [14]. Nonetheless, the influence of coffee consumption on the risk of arrhythmias remains a controversial issue. A large percentage of doctors recommend patients with heart palpitations to stop or reduce using coffee [15]. In a randomized clinical trial by Groh et al. [16], out of 957 patients with paroxysmal AF, 28% reported consumption of caffeine as a trigger for this arrhythmia.

Given the widespread consumption of coffee and the high prevalence of arrhythmias, this review summarizes the impact of consumption of this popular drink on the risk of cardiac arrhythmias.

Coffee — A brief overview

Worldwide, from the commercial point of view, the most important types are Arabica coffee (*Coffea arabica*), robusta coffee (*Coffea canephora*) and Liberian coffee (*Coffea liberica*) (Table 1) [17–19]. The largest amounts of coffee are produced in Brazil [20]. It is estimated that there are over 1000 chemical compounds in coffee. The most common chemical compounds in coffee are phenols (chlorogenic acid, and diterpenes: kahweol, and cafestol) and alkaloids (caffeine and trigonelline). Less abundant compounds found in coffee include mannose, polysaccharide chains of galactose, melanoidins, flavonoids, catechins, anthocyanins, ferulic acid, caffeic acid, p-coumaric acid, and tocopherols [21, 22].

The composition of coffee depends on many factors, including the type of coffee (e.g., *Coffea arabica*, *Coffea canephora*, *Coffea liberica*) (Table 1), the method of production (wet, dry, semi-dry/semi-

Table 1. Characteristics of *Coffea arabica*, *Coffea robusta*, and *Coffea liberica* [17–19]

Type of coffee/ characteristics	Place of cultivation	Bean	Percent in the global coffee market	Aroma	Mean concentration of chemical components [g/100 g]							
					Caffeine	Water	Proteins	Sucrose + reducing sugars	Poly-saccha- rides	Lipids	Chlorogenic acid	Minerals
<i>Coffea arabica</i>	Brazil, Central America and Africa		64%	++	1.6	8.0–12.0	9.8	8.1	49.8	16.2	6.5	4.2
<i>Coffea robusta</i>	Vietnam, Brazil, Indonesia and Africa		35%	+++	2.26	8.0–12.0	9.5	4.4	54.4	10.0	10.0	4.4
<i>Coffea liberica</i>	Malaysia, some regions of the Philippines and Africa (Liberia)		1%	+	1.23	11.0	14.0	8.0	42.0	12.0	7.0	4.0

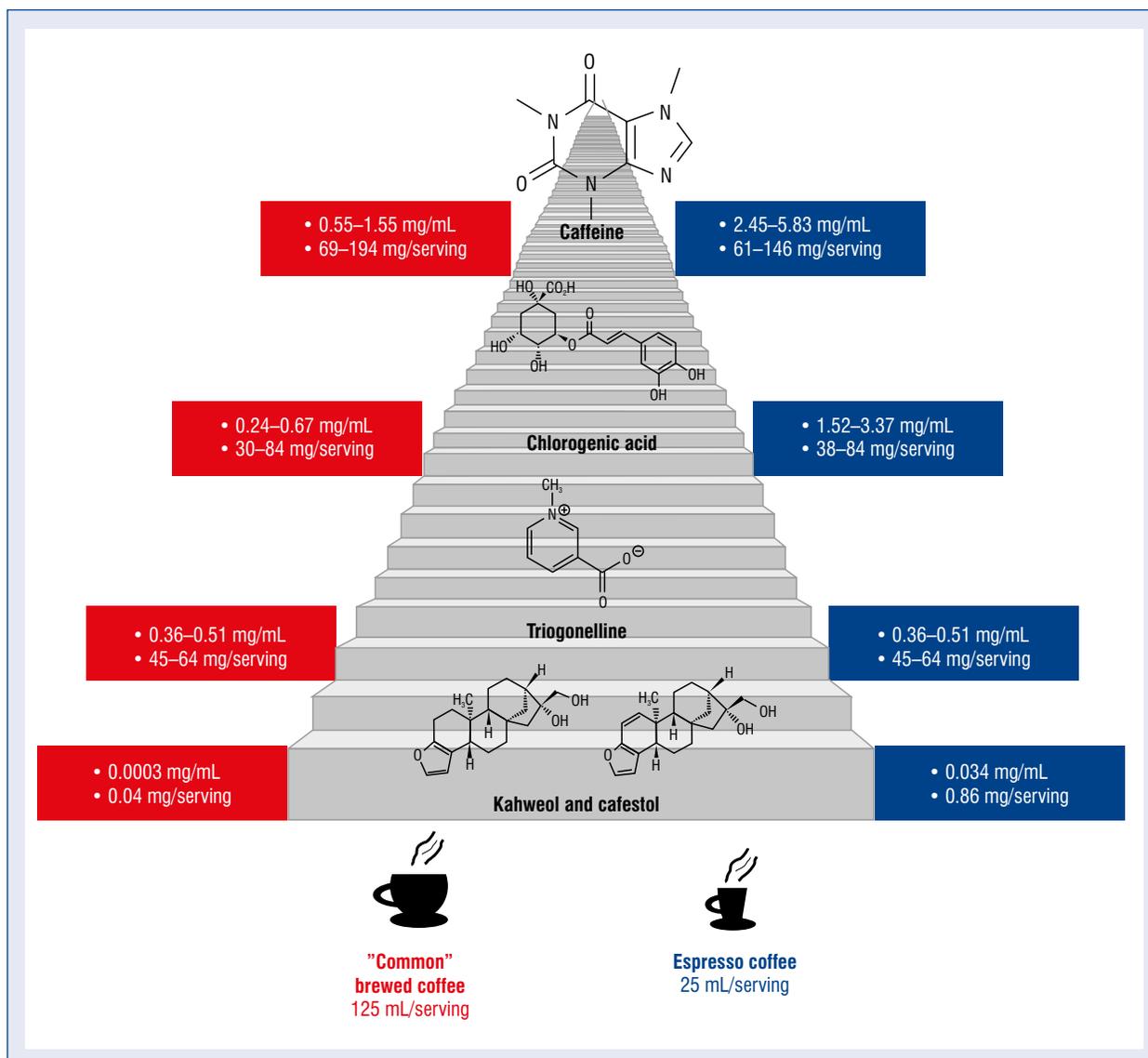
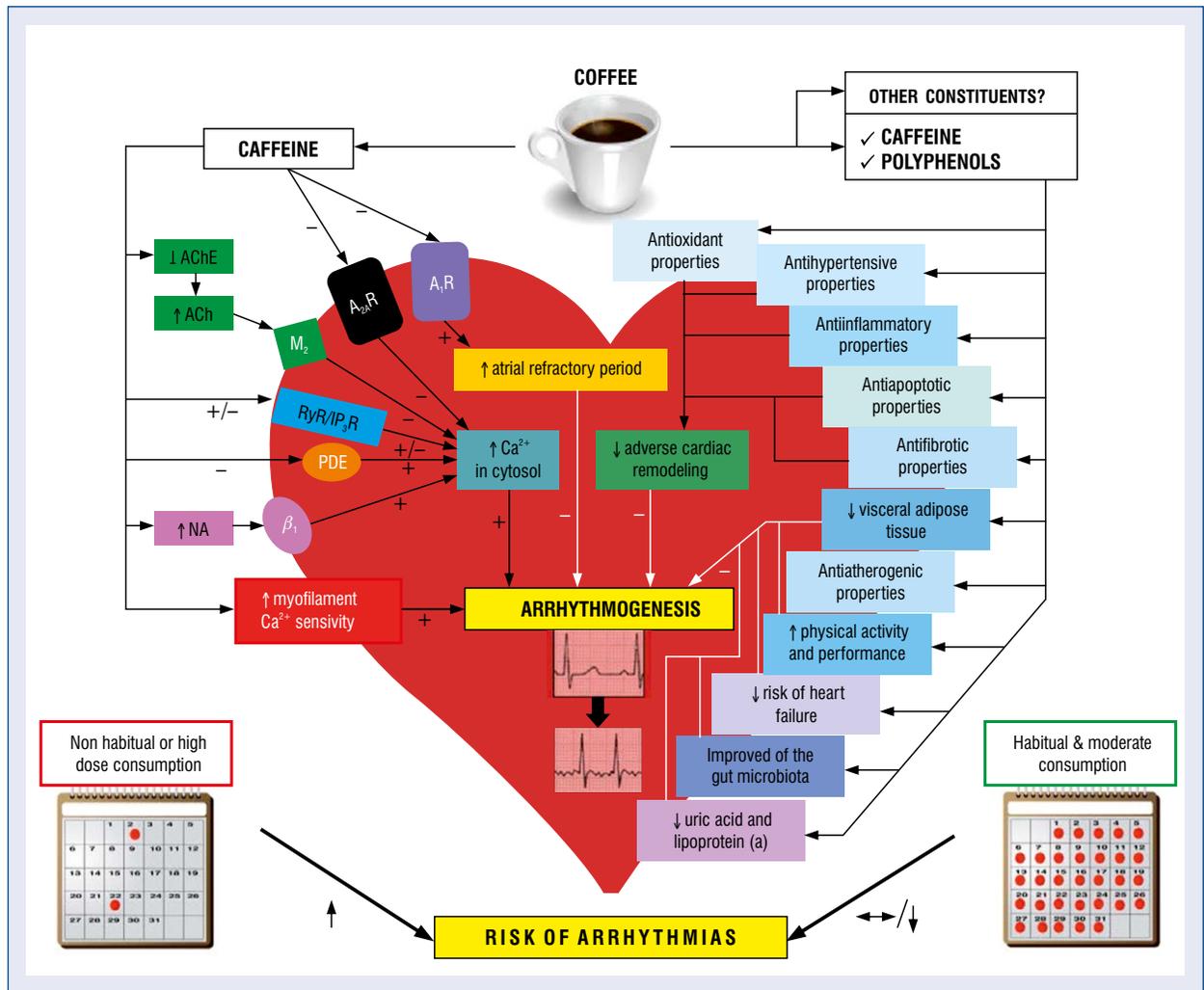


Figure 1. The main chemical compounds found in traditional coffee and espresso in terms of concentration and total amount in the usual serving sizes [20].

wet, and bio-processing), and the method of preparation (e.g., traditional brewed coffee, espresso) (Fig. 1) [17–19, 21–25]. Pre-harvest factors (e.g., sunlight) and post-harvest factors (e.g., method of processing coffee beans) account for approximately 40% and 60% of the organoleptic, physical, and chemical properties of coffee, respectively [17–19, 21–25]. Interestingly, the caffeine content in a cup of coffee varies by geographic region. In Northern Europe and the UK, a cup of coffee contains 140 mg of caffeine, in Southern Europe 50 mg, and in the USA 85 mg [26]. Caffeine is also found in drinks such as decaffeinated coffee, cola, green tea, black tea, and energy drinks [27].

Effect of chemical components in coffee on cardiac electrophysiology

Since it is likely that not all of the chemical compounds present in coffee have been identified, and that the mechanisms of action of most of the identified compounds are not yet fully understood, the biological properties of coffee are currently attributed to the effects of the best described compounds, such as caffeine, chlorogenic acid, trigonelline, cafestol, and kahweol, as well as ferulic acid. Central illustration summarizes the potential biochemical mechanisms of the influence of coffee on cardiac electrophysiology.



Central illustration. Effect of coffee on arrhythmogenesis; A₁R — adenosine A1 receptor; A_{2A}R — adenosine A2AR receptor; AChE — acetylcholinesterase; Ach — acetylcholine; M₂ — muscarinic acetylcholine receptor M₂; RyR — ryanodine receptors; IP₃R — inositol 1,4,5-trisphosphate receptor; PDE — phosphodiesterase; NA — noradrenaline; β₁ — β₁ adrenergic receptor.

Coffee is characterized by a very complex and poorly understood effect on the electrophysiology of the heart. There are pro- and anti-arrhythmic effects of coffee. It should be emphasized, however, that the observed effect depends on whether coffee is consumed occasionally or regularly and in what amounts [28].

Caffeine interacts with different receptors in the cardiovascular system in a dose dependent manner. Occasional or very high doses of caffeine consumption may increase the risk of arrhythmias because they may lead to phosphodiesterase (PDE) inhibition [29]. Inhibition of PDE leads to an increase in the level of cyclic adenosine monophosphate (cAMP) in the cardiomyocytes, which in turn results in the phosphorylation of protein

kinase A (PKA) [30]. Another caffeine mechanism increasing PKA phosphorylation in cardiomyocytes is the increase in noradrenaline (NA) release from sympathetic nerve endings [24]. NA, through β₁-adrenergic receptors, stimulating the production of cAMP [31]. PKA, by activating ryanodine receptors (RyR), stimulates the outflow of Ca²⁺ from the sarcoplasmic reticulum (SR) into the cytoplasm [31]. Interestingly, caffeine triggers Ca²⁺ release by reducing the threshold for luminal Ca²⁺ activation of RyR [32]. Thus, caffeine directly and indirectly increases the release of Ca²⁺ from SR. Increases in intracellular Ca²⁺ are potentially pro-arrhythmic through atrial pacemaker cell automaticity and after depolarization-induced triggered activity [33]. Another mechanism by which caffeine may increase

the risk of arrhythmia is by increasing myofilament Ca^{2+} sensitivity [28, 34].

On the other hand, caffeine is an inhibitor of acetylcholinesterase (AChE), which increases the concentration of acetylcholine (ACh), which, by stimulating the M_2 receptor, reduces the level of cAMP in the cell [35]. Moreover, caffeine can inhibit the activity of inositol 1,4,5-trisphosphate receptor (IP3R), which may reduce the influx of Ca^{2+} from SR into the cytoplasm [32].

Another important mechanism of caffeine's action is the non-selective antagonism of adenosine receptors (A_1R and $A_{2A}R$) [27]. In the atria, adenosine exerts direct and indirect anti- β -adrenergic effects. The activation of $I_{K_{\text{ado}}}$, *via* A_1R leads to shortening of action potential duration and refractoriness, thus facilitating reentry mechanisms and atrial arrhythmias. Overexpression of A_1R is associated with bradycardia, delayed conduction through the sinoatrial and atrioventricular nodes, atrial arrhythmia, and ventricular hypertrophy [36]. Adenosine, in turn, through $A_{2A}R$ stimulates the RyR that control part of the intracellular Ca^{2+} flux from the SR storage site [36]. Taking this into account, the non-selective antagonism of A_1R and $A_{2A}R$ by caffeine is characterized by antiarrhythmic activity, since it cannot only inhibit the onset of AF but can also impede its propagation throughout the atria *via* increased refractoriness.

Coffee is also characterized by a number of other important mechanisms of action that reduce the risk of arrhythmia, for example, antioxidant activity [37]. Indeed, coffee has a higher level of antioxidant activity (292 to 948 min) than black tea (67 to 277 min) or herbal tea (6 to 78 min), on the basis of a cup serving [38, 39]. Coffee (its chemical components) is also characterized by antihypertensive [3], anti-inflammatory [40, 41], anti-apoptotic [42], anti-fibrotic [43, 44] and anti-atherosclerotic [45–47] effects. Moreover, coffee consumption has been shown to reduce visceral adipose tissue, which is also characterized by an antiarrhythmic effect [48]. Clinical trials have shown that coffee consumption was associated with a reduced risk of heart failure (HF) [49]. It has also been suggested that the antiarrhythmic properties of coffee may result from its influence on the composition of the gut microbiota [50–52]. Chlorogenic acid may reduce the production of trimethylamine (TMA; precursor of arrhythmogenic trimethylamine N-oxide [TMAO]) [53], while coffee consumption may increase the level of *Bifidobacterium spp.* [54, 55] involved in the production of short-chain fatty

acids (SCFA), which may reduce the risk of arrhythmias [56]. It is worth mentioning that chlorogenic acid is an inhibitor of xanthine oxidase [57]. Therefore, consumption of coffee leads to a decrease in the level of uric acid, which is characterized by proarrhythmic properties [57, 58]. Coffee may also reduce the plasma concentration of lipoprotein (a) [Lp (a)], which may also contribute to reducing the risk of AF [59–61]. Coffee consumption contributes to an increase in physical activity and performance [62, 63], which also reduces the risk of arrhythmias [64].

In summary, coffee's mechanisms of action may both increase and decrease the risk of arrhythmias. It should be emphasized that regular consumption of moderate amounts of coffee leads to the development of tolerance, so that antiarrhythmic, long-term effects of coffee may become more important.

Coffee and arrhythmias — Clinical studies

The effect of coffee consumption on the risk of arrhythmia has been assessed in numerous clinical studies. The key studies on the effect of coffee consumption on the risk of arrhythmia are summarized in Table 2 [65–104].

As previously mentioned, the risk of arrhythmia may be related to the stimulation of the sympathetic nervous system, especially with large amounts of coffee. This is confirmed by experimental and clinical studies.

In a study by Strubelt and Diederich [105], the administration of 15 mg/kg/min caffeine resulted in sympathetic over-activation, with sinus tachycardia and ventricular ectopy culminating in ventricular fibrillation in all rats, and the effects were partially reversed by administration of β -adrenergic receptor antagonists. This was also confirmed by Robertson et al. [106] in which healthy subjects who did not consume coffee for 3 weeks were given 250 mg of caffeine (which corresponds to 3 cups of coffee) whereby a significant increase in the concentration of norepinephrine and adrenaline by 75% and 207%, respectively, was demonstrated.

The negative effect of a high dose of coffee on the risk of arrhythmias is confirmed by de Vreede-Swagemakers et al. [95] which found that only consumption of > 10 cups of coffee/day was associated with a significant increase in the risk of sudden cardiac death. Caffeine overdose can cause life-threatening arrhythmias [107]. A significant relationship between the pattern of coffee consumption and the risk of arrhythmia was demonstrated

Table 2. Major studies examining the impact of coffee/caffeine on risk of arrhythmias.

Author [Ref.] (year)	Study type	N (subjects)	Findings	Conclusion
Kistler et al. [65] (2022)	Observational	502,543 subjects (34,279 with CVD)	Follow-up: > 10 years. Coffee consumption at all levels (0, < 1, 1, 2–3, 4–5, > 5 cups/day) was not associated with risk of arrhythmia including AF/atrial flutter in those with CVD. Of 24111 patients diagnosed with an arrhythmia, coffee intake was associated with mortality reduction. Lowest risk was at 1 cup/day (HR = 0.85; 95% CI: 0.78–0.94). In those with AF/atrial flutter, 1 cup/day was associated with improved survival (HR = 0.82; 95% CI: 0.73–0.93)	↔
Marcus et al. [66] (2021)	Randomized controlled	320 subjects with paroxysmal AF	Follow-up: 10 weeks. Acute exposure to alcohol increased AF risk, with no evidence that other exposures, including caffeine, more commonly triggered AF	↔
Marcus et al. [67] (2021)	Randomized controlled	100 healthy subjects	Real-time coffee consumption (> 1 cup) had no significant impact on risk PAC	↔
Krittanawong et al. [68] (2021)	Meta-analysis	12 studies (361,143)	Coffee consumption is not associated with the risk of new-onset AF (NS)	↔
Bazal et al. [69] (2021)	Meta-analysis	2 cohorts (25,462)	Consumption of caffeinated coffee (1–7 cups/week) reduced the risk of AF (HR = 0.60; 95% CI: 0.44–0.82)	↓
Kim et al. [70] (2021)	Prospective cohort with Mendelian randomization	386,258 subjects	Follow-up: 4.5 ± 3.1 years. Each additional cup of habitual coffee consumed had a positive effect on the risk of AF and/or atrial flutter (HR = 0.97; 95% CI: 0.96–0.98)	↓
Signori et al. [71] (2021)	Randomized controlled	1227 subjects with HF	Follow-up: 3 months. The effect of coffee consumption on the risk of AF was dose-related: <ul style="list-style-type: none"> • 1–2 cups/day (NS) • ≥ 3 cups/day (HR = 0.21; 95% CI: 0.09–0.53) 	↔/↓
Yuan et al. [72] (2021)	Mendelian randomization	35,979 and 17,325 subjects	Coffee consumption is not associated with the risk of AF (UK Biobank and FinnGen consortium: NS)	↔
Yuan et al. [73] (2019)	Mendelian randomization	588,190 subjects	A causal relationship between habitual coffee consumption and the risk of AF has not been demonstrated (NS)	↔
Bodar et al. [74] (2019)	Prospective	18,960 males	Follow-up: 9 years. The effect of coffee consumption on the risk of AF was dose-related: <ul style="list-style-type: none"> • ≤ 1 cup/week (NS) • 2–4 cups/week (NS) • 5–6 cups/week (NS) • 1 cup/day (HR = 0.85; 95% CI: 0.74–0.98) • 2–3 cups/day (HR = 0.86; 95% CI: 0.76–0.97) • > 4 cups/day (NS) 	↔/↓
Xu et al. [75] (2019)	Observational	5972 subjects	Follow-up: 14 years. Nonhabitual (> 0–0.5 cups/day) consumption of coffee (HR = 1.22; 95% CI: 1.01–1.48) Habitual coffee consumption was not associated with AF risk (NS for ≥ 0.5–1.5 cups/day and NS for ≥ 1.5 cups/day)	↑/↔
Abdelfattah et al. [76] (2018)	Meta-analysis	8 studies (176,675)	The incidence of new-onset AF is not increased by coffee consumption (NS)	↔
Casiglia et al. [77] (2018)	Prospective cohort	1475 subjects	Follow-up: 12 years. Consumption of < 320 mg caffeine/day was not significantly associated with the risk reduction of AF, while consumption > 320 mg/day significantly reduced this risk, regardless of the CYP1A2 polymorphism (p = 0.008)	↔/↓

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Table 2 (cont.). Major studies examining the impact of coffee/caffeine on risk of arrhythmias.

Author [Ref.] (year)	Study type	N (subjects)	Findings	Conclusion
Mostofsky et al. [78] (2016)	Population-based cohort	57,053 subjects	Follow-up: 13.5 years. The effect of coffee consumption on the risk of AF was dose-related: <ul style="list-style-type: none"> • ≤ 1–5 cups/day (NS) • 6–7 cups/day (HR = 0.79; 95% CI: 0.64–0.98) • > 7 cups/day (NS) 	↔/↓
Dixit et al. [79] (2016)	Observational	1388 subjects	No correlation between atrial ectopics/h and intake of coffee (p = 0.28)	↔
Larsson et al. [80] (2015)	Meta-analysis	6 studies (248,910)	Highest vs. lowest category of coffee consumption (NS). Increment of coffee consumption per 2 cups/day (NS)	↔
Larsson et al. [80] (2015)	Population-based cohort	76,475 subjects	Follow-up: 12 years. Coffee consumption has not been shown to influence the risk of AF. <ul style="list-style-type: none"> • < 2–≥ 5 cups/day: HR = NS 	↔
Cheng et al. [81] (2014)	Meta-analysis	6 studies (228,465)	After smoking adjusting beneficial effect of coffee on the risk of AF: low dose of coffee (RR = 0.89; 95% CI: 0.80–0.99) and high dose of coffee (RR = 0.84; 95% CI: 0.75–0.94)	↓
Caldeira et al. [82] (2013)	Meta-analysis	7 studies (115,993)	Consumption of < 350 mg caffeine/day was associated with a 15% reduction in the risk of AF (OR = 0.85; 95% CI: 0.78–0.92)	↓
Klatsky et al. [83] (2011)	Retrospective population cohort	130,054 subjects	Follow-up: 17.6 years. In most cases, coffee consumption did not affect the risk of hospitalization for AF and atrial flutter: <ul style="list-style-type: none"> • < 1 cup/day (NS) • 1–3 cups/day (NS) • ≥ 4 cups/day (AF risk: HR = 0.81; 95% CI: 0.69–0.96; atrial flutter: NS) • Per cup per day (NS) 	↔/↓
Mattioli et al. [84] (2011)	Observational	247 hypertensive subjects	Consumption of 1– > 3 cups of coffee/day was not significantly associated with the risk of spontaneous conversion of AF	↔
Shen et al. [85] (2011)	Prospective cohort	4526 subjects	Consumption of caffeine was not significantly associated with AF risk. Q1, Q2, Q3 and Q4: NS	↔
Conen et al. [86] (2010)	Randomized controlled	33,638 women	Follow-up: 14.4 years. The effect of coffee consumption on the risk of AF was dose-related: <ul style="list-style-type: none"> • 0 to < 1 cup/day (NS) • 1 cup/day (NS) • 2–3 cups/day (RR = 1.36; 95% CI: 1.12–1.65) • ≥ 4 cups/day (NS) 	↑/↔
Mukamal et al. [87] (2009)	Prospective cohort	33,538 subjects with MI	Follow-up: 6.6–9.9 years. Coffee consumption ≥ 1 cup/day was not associated with adjusted HR for AF (HR = NS)	↔
Mattioli et al. [88] (2008)	Comparative	400 subjects	The effect of coffee consumption on the risk of AF was dose-related: <ul style="list-style-type: none"> • 1–3 cups/day (OR = 0.02; 95% CI: 0.013–0.086) • > 3 cups/day (OR = 3.14; 95% CI: 1.864–3.35) Consumption of > 3 cups of coffee/day was not significantly associated with the persistent AF	↑/↔/↓
Frost et al. [89] (2005)	Prospective cohort	47,949 subjects	Follow-up: 5.7 years. When the lowest quintile of caffeine consumption was used as a reference, the adjusted HR in quintiles 2, 3, 4, and 5 were insignificant	↔
Mattioli et al. [90] (2005)	Case control	116 subjects	High coffee intake, > 3 cups/day, was associated with a lower rate of spontaneous cardioversion from AF (OR = 0.3; 95% CI: 0.11–0.49)	↔



Table 2 (cont.). Major studies examining the impact of coffee/caffeine on risk of arrhythmias.

Author [Ref.] (year)	Study type	N (subjects)	Findings	Conclusion
Wilhelmsen et al. [91] (2001)	Population-based cohort	7495 subjects	Follow-up: 25.2 years. Consumption of ≥ 5 cups/day was not significantly associated with a higher risk of incident AF, although moderate consumption reached borderline significance (OR = 1.24; 95% CI: 1.00–1.54)	\leftrightarrow
Ventricular arrhythmia (VA)				
Marcus et al. [67] (2021)	Randomized controlled	100 healthy subjects	Real-time coffee consumption (> 1 cup) had no impact on risk of VT episodes. Consuming > 1 cup of coffee significantly increased the risk of PVC (consumption ≤ 1 cup did not increase this risk significantly). Moreover, faster caffeine metabolizers experienced a heightened risk of PVC	\leftrightarrow
Zuchinali et al. [92] (2016)	Meta-analysis	7 studies (290 subjects)	Coffee consumption did not affect the rate of ventricular premature beats (high dose: NS; low dose: NS)	\leftrightarrow
Zuchinali et al. [93] (2016)	Randomized controlled	51 subjects with HF	Acute caffeine ingestion (500 mg over 5 h) vs. placebo did not increase VPBs (185 vs. 239, respectively; $p = 0.47$) or nonsustained VT in patients with moderate to severe LV dysfunction	\leftrightarrow
Bertoia et al. [94] (2013)	Randomized controlled	93,676 post-menopausal women	Follow-up: 11 years. No association between coffee consumption ($p = 0.84$) and risk of sudden cardiac death	\leftrightarrow
Klatsky et al. [83] (2011)	Retrospective population cohort	4526 subjects	Follow-up: 17.6 years. In most cases, coffee consumption did not affect the risk of hospitalization for ventricular fibrillation/flutter/cardiac arrest: <ul style="list-style-type: none"> < 1 cup/day (NS) 1–3 cups/day (NS) ≥ 4 cups/day (HR = 0.47; 95% CI: 0.23–0.96) Per cup per day (NS) 	$\leftrightarrow/\downarrow$
de Vreede-Swagemakers et al. [95] (1999)	Case control	117 subjects with CAD	Only very heavy coffee consumption (> 10 cups/day) was associated with a higher risk of sudden cardiac arrest (OR = 55.7; 95% CI: 6.4–483). Consumption 1–9 cups of coffee/day was not a significant risk factor	\uparrow/\leftrightarrow
Newby et al. [96] (1996)	Randomized controlled	13 subjects with idiopathic VPB	Follow-up: 6 weeks. No significant changes in palpitation scores or VPB frequencies during the intervention weeks and no significant correlations were found between these variables and serum caffeine concentrations	\leftrightarrow
Myers et al. [97] (1990)	Randomized controlled	35 subjects with MI	Moderately high doses of caffeine (450 mg/day) do not appear to increase ventricular arrhythmias	\leftrightarrow
Graboyes et al. [98] (1989)	Crossover	50 subjects with malignant VA	In subjects with structural heart disease, hourly VPBs burden and nonsustained VT did not differ between the caffeine and placebo	\leftrightarrow
Myers et al. [99] (1987)	Randomized controlled	70 subjects	In 7-day post-MI patients, continuous Holter monitoring did not show a difference in percentage of patients who had VPBs, nor VPB burden after 300 mg of caffeine vs. placebo	\leftrightarrow
Prineas et al. [100] (1980)	Cross-sectional	7311 subjects	Compared with consumption of ≤ 2 cups of coffee/day ($t = 2.90$; $p < 0.005$) was positively associated with the presence of VPBs, with > 9 cups of coffee associated with twice the risk of VPBs in healthy subjects	\uparrow

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Table 2 (cont.). Major studies examining the impact of coffee/caffeine on risk of arrhythmias.

Author [Ref.] (year)	Study type	N (subjects)	Findings	Conclusion
Tachyarrhythmias				
Kim et al. [70] (2021)	Prospective cohort with Mendelian randomization	386,258 subjects	Follow-up: 4.5 ± 3.1 years. Each additional cup of habitual coffee consumed was inversely associated with the risk of SVT (HR = 0.96; 95% CI: 0.94–0.99)	↓
Marcus et al. [67] (2021)	Randomized controlled	100 healthy subjects	Real-time coffee consumption (> 1 cup) had no impact on risk of SVT episodes	↔
de Oliveira et al. [101] (2017)	Cross-sectional	15,105 subjects	Follow-up: 12 months. The association between coffee consumption and HRV reduction disappears for HRV indexes after adjusting for potential confounding factors	↔
Dixit et al. [79] (2016)	Observational	1388 subjects	No correlation between supraventricular tachycardia runs and intake of coffee (p = 0.22)	↔
Lemery et al. [102] (2015)	Prospective randomized controlled	80 subjects with symptomatic SVT	Caffeine 5 mg/kg bw (moderate intake) or placebo. Electrocardiography examination after 57 ± 13 min after caffeine consumption. <ul style="list-style-type: none"> • Heart rate (NS difference) • Effective refractory period of atrium or ventricle (NS difference) • Atrioventricular node conduction (NS difference) • SVT (NS difference) 	↔
Notarius et al. [103] (2012)	Randomized controlled	21 subjects	Caffeine enhances cardiac parasympathetic activity and reduces sympathetic outflow to the skeletal muscle in middle-aged healthy subjects, but has no effects on HRV or MSNA in CHF subjects	↔/↓
Klatsky et al. [83] (2011)	Retrospective population cohort	4526 subjects	Follow-up: 17.6 years. In most cases, coffee consumption did not affect the risk of hospitalization for PST and PVT: <ul style="list-style-type: none"> • < 1 cup/day (NS) • 1–3 cups/day (NS) • ≥ 4 cups/day (PVT risk: HR = 0.63; 95% CI: 0.41–0.98; PST: NS) • Per cup per day (NS) 	↔/↓
Richardson et al. [104] (2009)	Randomized controlled	103 subjects with STEMI	Follow-up: 5 days. There was no detrimental effect of regular coffee consumption on cardiac rhythm post-STEMI	↔

AF — atrial fibrillation; CAD — coronary artery disease; CHF — congestive heart failure; CI — confidence interval; CVD — cardiovascular disease; HF — heart failure; HR — hazard ratio; HRV — heart rate variability; LV — left ventricle; MI — myocardial infarction; MSNA — muscle sympathetic nerve activity; NS — not significant; OR — odds ratio; PAC — premature atrial contractions; PST — paroxysmal supraventricular tachycardia; PVC — premature ventricular contractions; PVT — paroxysmal ventricular tachycardia; Q — quartile; RR — relative risk; STEMI — ST-segment elevation myocardial infarction; SVT — supraventricular tachycardia; VPB — ventricular premature beats; VT — ventricular tachycardia

by Xu et al. [75] whereby subjects who consumed coffee in a non-habitual manner had a 22% higher risk of AF than those who did not consume coffee. Such a relationship has not been demonstrated in subjects habitually consuming coffee [75].

In a prospective Mendelian randomized controlled trial by Kim et al. [70] the influence of coffee consumption on the incident tachyarrhythmias was assessed. The study covered 386,258 subjects, who were followed on average for 4.5 years. Habitual coffee consumption was found to be associated

with a significant, but small, reduction in the risk of incident arrhythmia (hazard ratio [HR] = 0.97; 95% confidence interval [CI]: 0.96–0.98, p < 0.001). The analysis by type of arrhythmia also showed a similar effect of habitual coffee consumption on the risk of AF and/or atrial flutter (HR = 0.97; 95% CI: 0.96–0.98, p < 0.001) and supraventricular tachycardia (HR = 0.96; 95% CI: 0.94–0.99, p = 0.002) [70].

The influence of habitual coffee consumption on the risk of ventricular tachycardia, premature

atrial complex and premature ventricular complex has not been demonstrated. Importantly, Mendelian randomization failed to provide evidence that caffeine consumption was associated with arrhythmias [70]. In a randomized clinical trial, involving 320 patients with paroxysmal AF followed-up for 10 weeks, acute exposure to alcohol increased AF risk, but no such effect of caffeine consumption was shown [66]. Another randomized study, Coffee And Real-time Atrial And Ventricular Ectopy (CRAVE) involving 100 healthy subjects followed for 13.3 days, assessed the effect of coffee consumption on the risk of real-time arrhythmias [67]. Consumption of > 1 cup of coffee/day had no effect on the risk of premature atrial contractions (relative risk [RR] = 0.81; 95% CI: 0.51–1.29), supraventricular tachycardia (RR = 0.83; 95% CI: 0.63–1.10) and ventricular tachycardia. However, consumption of > 1 cup of coffee/day increased the risk of premature ventricular contractions (RR = 2.20; 95% CI: 1.24–3.92), especially in intermediate and fast caffeine metabolizers. Of note, they studied acute effects, and included healthy volunteers (not arrhythmia patients), participants were not blinded to the intervention, did not have continuous electrocardiography rhythms and that genetic variants or other behaviors may modify the observed effects [67].

In a randomized study by Zuchinali et al. [93] including 51 patients with HF, acute caffeine ingestion (500 mg over 5 h) vs. placebo did not increase ventricular premature beats. Interestingly, a randomized study involving 1227 patients with HF who were followed for 3 months, found that coffee consumption (≥ 3 cups/day) may reduce the risk of AF [71]. Similar results were obtained by Bodar et al. [74], who studied 18,960 males followed for 9 years, whereby consumption of 2–3 cups of coffee/day reduced the risk of AF occurrence. On the other hand, Mendelian randomized studies [72, 73] showed no association between coffee consumption and the risk of AF. In a prospective study involving 1475 participants followed for 12 years, caffeine consumption > 320 mg/day significantly reduced the risk of AF, regardless of the *CYP1A2* polymorphism ($p = 0.008$) [77].

The relationship between coffee consumption and the risk of arrhythmias has been summarized in several meta-analyses. In a meta-analysis of 12 clinical trials, no effect of coffee consumption on the risk of new-onset AF was found [68]. The same results were obtained in another meta-analysis of 8 studies by Abdelfattah et al. [76]. Moreover, a meta-analysis of 2 studies by Bazal et al. [69] found that coffee consumption (1–7 cups/week

may reduce the risk of AF. The beneficial effect of coffee consumption were also found in previous meta-analyses by Cheng et al. [81], and Caldeira et al. [82]. With regard to ventricular arrhythmias, a meta-analysis of 7 studies by Zuchinali et al. [92] did not show that coffee consumption influenced of rate of ventricular premature beats.

The study by Kistler et al. [65], which included 502,543 subjects from UK Biobank, showed that regular coffee intake is shown to be safe in prevalent cardiovascular disease with no increase in risk of arrhythmia. Survival benefit with coffee intake was observed in those with prevalent arrhythmia. Thus, coffee should not be discouraged in patients with prevalent cardiovascular disease and arrhythmia.

Aside from arrhythmias, the Coronary Artery Risk Development in Young Adults (CARDIA) clinical study showed that low-to-moderate daily coffee consumption from early adulthood to middle age was associated with better left ventricular systolic and diastolic function in midlife [108]. High daily coffee consumption (> 4 cups/day) was associated with worse left ventricular function, while there was no association between pure caffeine or tea intake and cardiac function [108].

In conclusion, the results of numerous clinical trials (randomized, prospective, randomized Mendelian, etc.) and meta-analyses indicate that habitual consumption of coffee in moderate amounts (2–3 cups of coffee/day) does not increase the risk of arrhythmia, and might even reduce it slightly. While coffee consumption may increase the risk of premature ventricular contractions, these results are inconsistent and require further study.

Limitations of research on the effect of coffee on arrhythmias

The most important limitation of studies thus far is that it is not known exactly which coffee was consumed by the participants (type, blend, country of origin, type of grain treatment, preparation method, additives — milk and/or sugar, and the different definitions of a cup of coffee). As discussed, many factors influence the biological properties of coffee. Another limitation is the influence of the diet of the respondents, as well as polymorphisms of numerous genes of enzymes involved in the metabolism of coffee chemical components (these polymorphisms may differ between the participants of the cited studies), which may cause different sensitivity of the respondents to coffee and thus the occurrence of various biological effects after its consumption.

Another limitation is that some studies have used caffeine instead of coffee, which only allows indirect conclusions about how coffee works. The reason is the presence of many other chemical compounds in coffee, which are also biologically active. Recently, an important role of epigenetics has been pointed out, which would explain the different effects of coffee observed in various studies (coffee consumption is associated with different levels of DNA methylation in many CpG sites) [109].

Also, most meta-analyses are based on the results of observational studies, which makes it impossible to assess the cause-and-effect relationship. All this means that the possibility of interpreting and comparing the results is limited. Of note, people tend to naturally regulate their coffee consumption based on blood pressure levels and heart rate, hence observational studies of habitual coffee intakes are prone to influences by reverse causation, and caution is required when inferred health benefits result from comparisons with coffee abstainers or decaffeinated coffee drinkers [110].

Conclusions and clinical perspectives

Based on the present literature review, consuming 2–3 cups of black coffee (without milk and sugar) daily should not increase arrhythmias in the general population. Separate studies, however, are awaited in some populations, such as those with paroxysmal AF, HF with reduced ejection fraction, those after different arrhythmia ablation procedures, etc. Moreover, there are a lack of data on the safety of coffee consumption by patients after AF ablation. In some subpopulations, such as pregnant women, coffee consumption remains controversial and should be closely monitored [111]. As so many beneficial effects of coffee drinking have been researched on, the cardiovascular perspective on coffee has improved over the years, and we are perhaps looking at coffee more as a friend than foe.

Conflict of interest: None declared

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