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CLINICAL RESEARCH

Tobacco-related cardiovascular risk in women: New issues and therapeutic perspectives

Le risque cardiovasculaire lié au tabac chez les femmes : nouveaux enjeux et perspectives thérapeutiques

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KEYWORDS
Women;
Stroke;

Summary
Background. — Smoking is the main modifiable risk factor for stroke and myocardial infarction, particularly in women; its prevalence in France is evolving, and new patterns of nicotine consumption have emerged.

Abbreviations: CI, confidence interval; CO, carbon monoxide; cpd, cigarettes per day; CVD, cardiovascular disease; MI, myocardial infarction; OCP, oral contraceptive pill.

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Myocardial infarction;
Tobacco;
Electronic cigarette

Aims. — To present contemporary data on smoking prevalence and the use of electronic cigarettes, and to describe current knowledge of the cardiovascular risk specificities and the effectiveness of withdrawal methods in women.
Method. — We identified studies by searching the MEDLINE bibliographic database between 1995 and 2020, and the Weekly Epidemiological Bulletin (Bulletin Épidémiologique Hebdomadaire) published by the French health authorities.
Result. — In recent years, smoking prevalence among French women has decreased overall, except in the oldest age group (aged > 55 years). At the same time, the incidence of hospitalization for cardiovascular events has increased worryingly among women smokers aged < 65 years. Active smoking in women is associated with an increased risk of premature myocardial infarction, and a risk of stroke that increases with the number of cigarettes consumed per day; it is also responsible for increased cardiovascular events in women taking oestrogen-progestin contraception. Quitting smoking reverses these effects in the long term, and women are just as likely to quit smoking as men.
Conclusions. — Stopping smoking must be a priority objective for women smokers, for primary and secondary prevention, and they should systematically be offered a validated method of cessation or even electronic cigarettes.

MOTS CLÉS
Femmes ;
Accident vasculaire cérébral ;
Infarctus du myocarde ;
Tabac ;
Cigarette électronique

Résumé
Contexte. — Le tabagisme représente un facteur de risque majeur et modifiable d'accident vasculaire cérébral et d'infarctus du myocarde, en particulier chez les femmes. Sa prévalence en France est en baisse et de nouveaux modes de consommation de nicotine sont apparus.
Objectif. — Présenter les données récentes sur la prévalence tabagique et l'utilisation de la cigarette électronique, décrire l'état des connaissances sur les spécificités du risque cardiovasculaire et présenter l'efficacité des méthodes de sevrage chez les femmes.
Méthodes. — Nous avons identifié les travaux menés entre 1995 et 2020 sur ce thème dans la base bibliographique MEDLINE et le Bulletin Epidémiologique Hebdomadaire.
Résultats. — Chez les Françaises, la prévalence tabagique a globalement diminué, sauf chez les plus âgées (> 55 ans). En parallèle, l'incidence des hospitalisations pour accident cardiovasculaire a connu une augmentation inquiétante chez les fumeuses de moins de 65 ans. Le tabagisme actif est associé chez les femmes à une augmentation du risque d'infarctus du myocarde prématuré et à un risque d'accident vasculaire cérébral qui s'accroît avec le nombre de cigarettes consommées par jour. Il est également responsable d'un sur-risque cardiovasculaire chez les femmes sous contraception œstroprogestative. Arrêter le tabac annule à long terme ces effets et les femmes ont autant de chances d'arrêter de fumer que les hommes.
Conclusions. — L'arrêt du tabac doit constituer un objectif prioritaire chez les fumeuses, en prévention primaire et secondaire en proposant systématiquement une méthode de sevrage validée voire la cigarette électronique.

Background

In women, smoking, like diabetes, is particularly harmful to the cardiovascular system, and is now a major risk factor for stroke and myocardial infarction (MI), both before and after menopause [1]. These conditions are a leading cause of death in French women, and the number of hospitalizations and deaths as a result of MI is increasing, particularly among women aged < 65 years [2]. In this review, we will describe recent trends in tobacco consumption and the use of electronic cigarettes among French women, and will specify their effects on the occurrence of MI and stroke. Finally, we will present the different smoking cessation methods, and summarize current knowledge regarding their effectiveness in this population.

Methods

For this review, we identified stroke, MI and tobacco studies published between 1995 and 2020 using the MEDLINE database (PubMed; National Library of Medicine, NIH, Bethesda, MD, USA) and the Weekly Epidemiological Bulletin (Bulletin Épidémiologique Hebdomadaire, a peer-reviewed

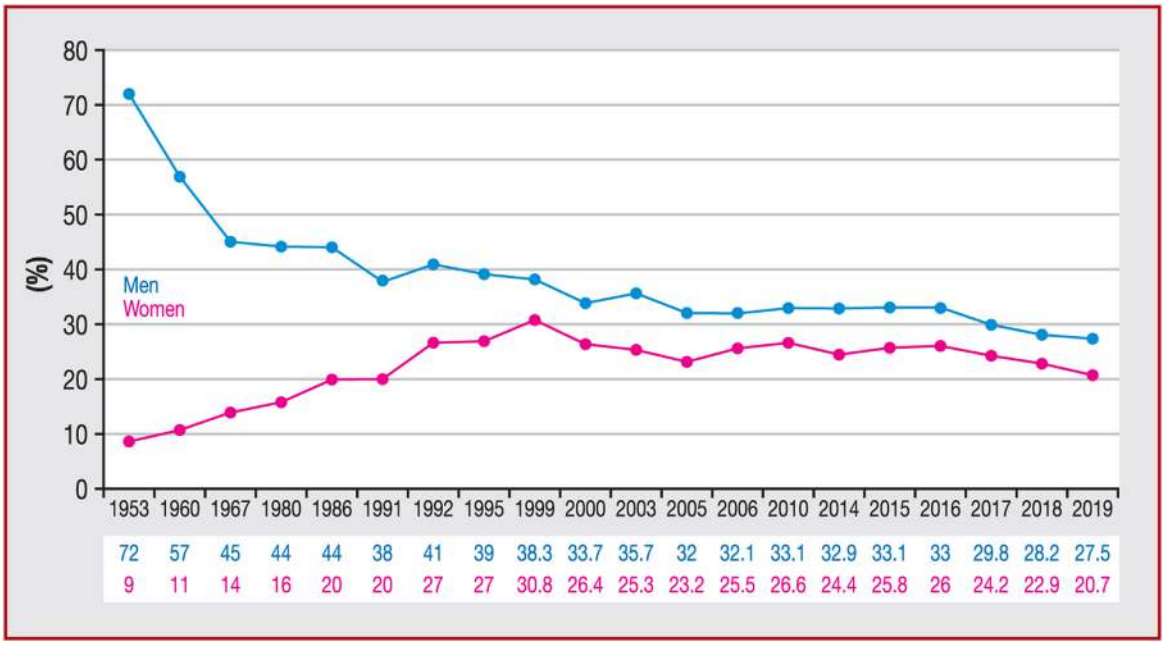

Figure 1. Change in the prevalence of regular or daily tobacco use in France between 1953 and 2019, among men and women. Adapted from Bulletin Épidémiologique Hebdomadaire (BEH) and Institut National de la Statistique et des Études Économiques (INSEE) publications.

journal published by Santé publique France). We conducted our search in three parts, as detailed below.

Part I (prevalence): smoking OR tobacco OR cigarette OR electronic cigarette OR e-cigarette OR vaping OR electronic nicotine delivery system OR electrically heated cigarette) AND (women OR female OR sex OR gender).

Part II (cardiovascular effects): key words from part I AND (cardiovascular disease OR heart disease OR myocardial infarction OR acute coronary syndrome OR ischemic heart disease OR stroke) AND (''Contraceptives, Oral, Combined''[Mesh] OR ''Contraceptives, Oral''[Mesh] OR ''Contraceptives, Oral, hormonal''[Mesh] OR ''Contraceptives, Oral, Combined''[Pharmacological Action] OR (contracept* AND (oral OR pill OR tablet)) OR ((combined hormonal) OR (combined oral) AND contracept*))).

Part III (smoking cessation): key words from parts I and II AND (smoking cessation OR quit attempt OR abstinence OR NRT OR nicotine replacement therapy OR varenicline OR bupropion OR TCC OR cognitive behavioural therapy).

In the Bulletin Épidémiologique Hebdomadaire, we searched for French publications on tobacco and/or cardiovascular disease (CVD); we then selected studies performed exclusively in women or that compared women with men. Studies in pregnant women were excluded.

Definition of variables related to tobacco and tobacco products

For tobacco products, we selected all products containing tobacco (manufactured cigarette, rolled cigarette, pipe, cigarillo, chicha, heated tobacco, unsmoked tobacco). For electronic cigarettes, we retained: (1) devices with a resistance and containing liquids with or without nicotine (electronic cigarettes or ''vaporizers'' or ''sprays''); and (2) closed-system devices that use disposable pods containing flavoured liquids and nicotine salts, with the appearance of a USB key.

Results and discussion

National epidemiological data

Prevalence and evolution of smoking

Whereas smoking in France has decreased markedly among men since the 1970s, there has been an increase in consumption among women, which persists today in certain age groups. Between 1953 and 2000, although the prevalence of daily smoking among adults aged 15 to 75 years had fallen in men (from 72% to < 40%), it increased from 17% to about 30% in women [3]. Between 2000 and 2015, daily smoking prevalence decreased among women aged < 45 years, but increased alarmingly among women aged > 45 years because of a generational effect (Fig. 1) [4].

However, between 2014 and 2019, a marked decline in the prevalence of daily smoking (from 24.4% to 20.7%) was observed for women in all age groups, except in those aged > 55 years, among whom the prevalence remained stable [5]. During this period, the number of cigarettes per day (cpd) also decreased among women (from 12.0 to 11.4 cpd), and remains lower than that observed among men (in whom the decrease was from 14.6 to 13.5 cpd) [4,5]. This decrease in consumption is related to the implementation of public health measures, which have also led to an increase in the age at which adolescent girls take up smoking [6]. Indeed, the age of consumption of a first cigarette went up from 14 years in 2014 to 14.4 years in 2017 [6].

The consumption of rolled tobacco, mainly among young people, increased between 2005 and 2018, as a result of

taxation being lower than that for manufactured cigarettes [7]. However, roll-your-own tobacco is used much less by women than by men, and cigarillos and cigars are consumed almost exclusively by men. Unsmoked tobacco is finely ground tobacco placed in the nose (dry snuff) or between the cheek and the gum (moist snuff, snus, chewing tobacco) of practitioners of winter sports (skiing, ice-hockey); it is rarely consumed in France, and twice less frequently by women than men [7].

The consumption of chicha (hookah, shisha, hooka or water pipe), once consumed exclusively in North Africa and South Asia, is now increasing among adolescent girls, because it is incorrectly considered to be a safer alternative to smoking. In the large ESCAPAD survey, nearly two thirds (63.2%) of 17-year-old French girls had already tried it, and nearly one in five (18.3%) were regular chicha users in 2014, much fewer than boys (32.1%) although trends decreased in 2017 [8].

Heated tobacco, a new product promoted by the tobacco industry to gradually replace smoked tobacco, has been on the national market since the late 1990s; it is consumed using a battery-operated device that heats tobacco to temperatures ranging from 180 °C to 340 °C to produce an inhalable aerosol [7]. Emissions from this device contain volatile organic compounds, polycyclic aromatic hydrocarbons and carbon monoxide (CO), which are toxic substances found in tobacco smoke [9]. The rate of use of heated tobacco by French women is not yet known.

Prevalence of electronic cigarette use

The marketing of electronic cigarettes, whether using nicotine liquids or not, has been authorized on the French market since 2010, and that of electronic cigarettes containing nicotine salts since 2018. In Europe, the concentration of nicotine in these devices may not exceed 20 mg/mL, to limit their addictive effect. In France, electronic cigarettes are used less frequently by women than by men. Between 2014 and 2016, among women aged 15—75 years, the prevalence of daily use remained stable, but occasional use fell by 50% (from 5.2% to 2.6%) [10]. In 2017, the frequency of daily use by French women aged $\geq$ 18 years was estimated to be 2.1% [11]. In the same year, nearly half (48.1%) of French girls aged 17 years had already tried an electronic cigarette, and 1% were daily users, compared with 56.5% and 2.8% of French boys aged 17 years, respectively [12].

Specific tobacco-related cardiovascular risk in women

Risk of stroke and MI

In France (excluding Mayotte), between 2008 and 2014, the incidence of stroke increased among women aged < 65 years [13]. In this age group, active or former smoking accounts for approximately 58% of strokes [14]. Thus, smoking is a major factor in the development of stroke. Also, the number of hospitalizations for MI among women aged 45—55 years has increased significantly, with a steady increase of 4.8% per year between 2008 and 2013 [15]. According to the INTERHEART study, carried out in 52 countries, active smoking in women increased the risk of premature MI (before the age of 66 years) by 4.49 (95% confidence interval [CI] 3.11 to 6.47) in smokers compared with non-smokers [16]. Fig. 2 summarizes these specific tobacco-related cardiovascular risks in women in comparison with men.

Risk of sudden death

Over 38 years of follow-up in the Framingham Study cohort, including 5209 men and women aged 30—62 years, cigarette smoking was a weak risk factor for sudden death in women at all ages [17]. In women followed in the Nurses' Health Study, smoking 1—14 cpd was associated with a 1.86 (95% CI 1.17 to 2.96) increased risk of sudden cardiac death, and every 5 years of continued smoking was associated with an 8% increased risk of sudden cardiac death (hazard ratio 1.08, 95% CI 1.05 to 1.12) [18].

Cardiovascular effects of electronic cigarette use

Little is known about the cardiovascular impact of the use of electronic cigarettes, and there are no studies to date indicating a specific effect in women. Similarly, the cardiovascular impact of dual use (cigarettes and electronic cigarettes), which is very common, regardless of sex, remains to be evaluated, in particular regarding conflict of interest [19]. Recent data indicate that certain chemicals, such as acrolein or aldehydes, in the aerosol emitted during the use of electronic cigarettes are associated with an increase in blood pressure and arterial stiffness, via an increase in oxidative stress [20]. We do not yet know if these changes in intermediate endpoints can have an impact on clinical events over time.

Cardiovascular risk, female hormones and oestrogen-progestin contraception

Combined oestrogen-progestin oral contraceptive pills (OCPs) are the most widely used form of contraceptive in France. Whether oestrogen-progestin is used orally, in a patch or in ring form, it increases the risk of both venous and arterial thrombotic events [21]. This risk mainly results from the procoagulant action of the hepatic metabolite of ethinylestradiol, which is increased by smoking, especially after the age of 35 years [22]. A large study covering the Oxford region among young women without cardiovascular risk factors highlighted a low rate of fatal cardiovascular events associated with OCP use, which was much lower than that driven by smoking. The combination of smoking and OCP use, particularly at older ages, was associated with a marked increase in cardiovascular risk [22]. Compared with non-smoking women who do not use OCPs, the risk of ischaemic stroke in women who smoke gradually increases with the number of cpd [21]. Therefore, smoking cessation should be a priority for women taking oestrogen-progestin.

Beyond the cardiovascular risk in women smokers, OCP use appears to affect a variety of smoking-related outcomes, including nicotine metabolism, mood, craving and withdrawal [23]. A review on hormonal contraception among electronic cigarette users has identified no evidence on cardiovascular outcomes, but the risk of this association needs further investigation [24]. Smoking is associated with early

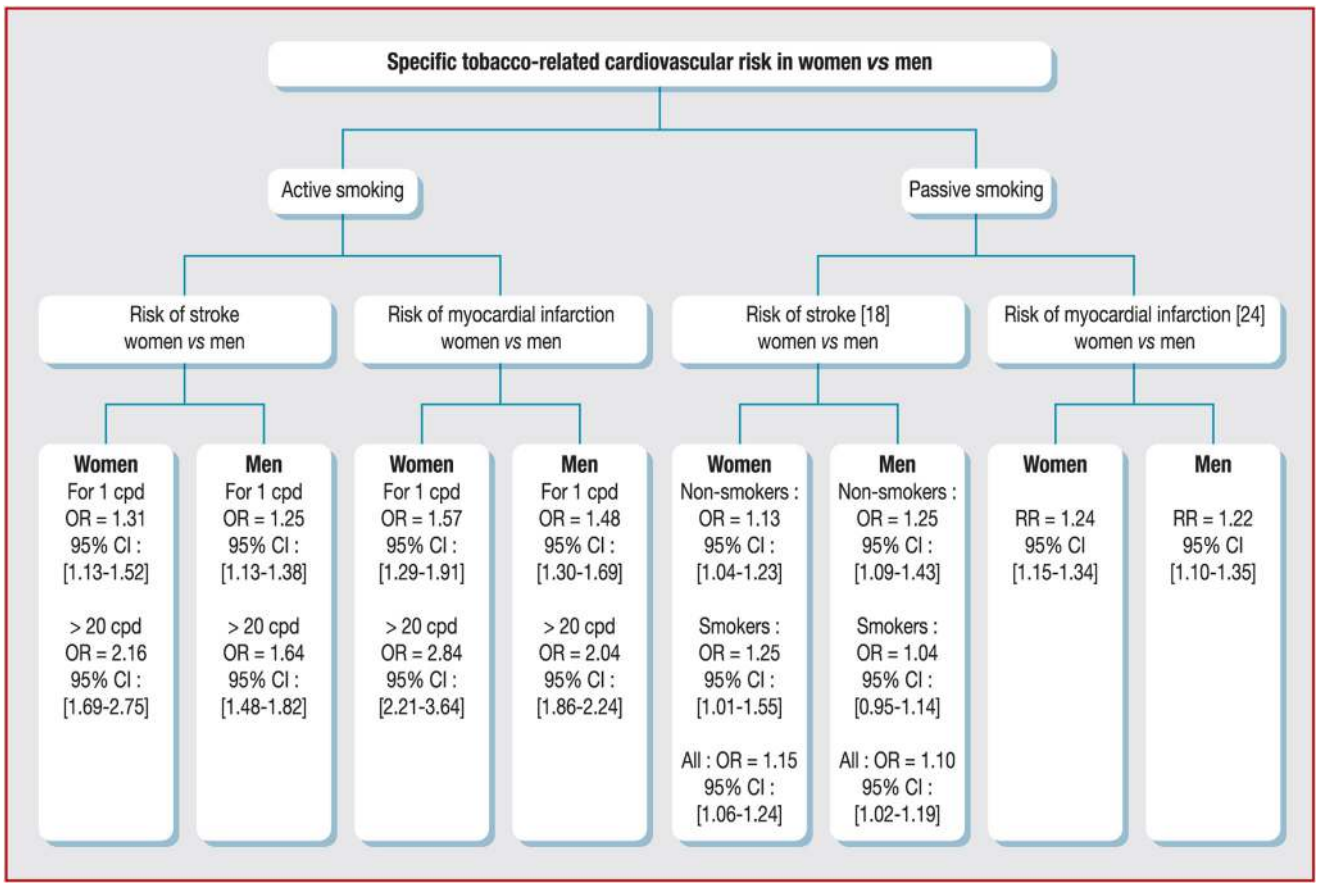

Figure 2. Specific tobacco-related cardiovascular risk in women compared with men [18,24,39—41]. cpd: cigarettes per day; CI: confidence interval; OR: odds ratio; RR: relative risk.

menopause and, in post-menopausal women, with a lower oestrogen level than in non-smoking women [25].

Mechanisms of tobacco's cardiovascular effects, and specificities in women

The cardiovascular effects of tobacco are numerous, promoting the development of atheromatous plaques, and precipitating the occurrence of acute atherothrombotic events. Tobacco smoke contains more than 4000 gaseous and/or particulate components, three of which (nicotine, CO and oxidizing gases) are particularly toxic to the cardiovascular system. Nicotine, as an addictive substance, is a sympathomimetic agent that, by binding to nicotine cholinergic receptors, stimulates the release of neuronal and adrenal catecholamines. Thus, it induces an increase in heart rate and output, blood pressure and myocardial contractility, which increases effort and myocardial oxygen demand. In experimental and human models, nicotine, by reducing the availability of nitric oxide and endothelium-dependent vasodilation, leads to endothelial dysfunction, a key step in the initiation and progression of atheroma, which promotes a proinflammatory and prothrombogenic state. Cigarette smoke induces a decrease in blood flow of in the coronary arteries by increasing total and epicardial vascular resistance, and increases the risk of vasospastic angina. In addition, tobacco nicotine increases the risk of metabolic abnormalities associated with cardiovascular risk. It may promote a state of insulin resistance and changes in circulating lipids, mainly through an increase in triglycerides and low-density lipoprotein cholesterol, and a decrease in high-density lipoprotein cholesterol.

CO, a product of incomplete combustion of tobacco, with a higher affinity than oxygen for haemoglobin, decreases tissue oxygenation. In smokers, the moderate hypoxaemia associated with chronic exposure to CO induces an increase in erythrocyte mass and blood hyperviscosity, promoting a state of hypercoagulability, which could aggravate ischaemic lesions.

Finally, oxidizing gases, such as nitrogen oxides, through the production of reactive oxygen species, are responsible for oxidative stress, inducing endothelial dysfunction, oxidized low-density lipoprotein formation, platelet activation and increased fibrinogen—conditions that promote a chronic and prothrombotic inflammatory state.

Although the underlying mechanisms explaining the specific sensitivity of the female cardiovascular system to tobacco remains poorly understood, they are believed to be partly based on nicotine metabolism. Pharmacological studies show that women have a faster nicotine metabolism, which is linked to stimulation of cytochrome P450 2A6 activity [26]. Sex hormones, particularly oestrogens, and

Table 1 Benefits of smoking cessation after stroke and/or myocardial infarction[a].

Reference; country	Type of study	Objectives	Patients; follow-up; outcome measures	Results	Conclusions
Chen et al., 2019 [46]; People's Republic of China	Observational cohort study	To estimate the impact of smoking status on the risk of stroke recurrence, and determine whether a dose-response relationship exists	3069 (27.8% women); duration of follow-up = 2.4 ± 1.2 years; primary endpoint = fatal or non-fatal recurrent stroke 3 months after the index stroke	Risk of stroke: former smokers vs. non-smokers, HR 1.26 (95% CI 0.82 to 1.93); quitters vs. non-smokers, HR 1.20 (95% CI 0.90 to 1.60); persistent smokers vs. non-smokers, HR 1.52 (95% CI 1.13 to 2.05)	After an initial stroke, persistent smoking increases the risk of stroke recurrence
Critchley et al., 2003 [47]; UK	Systematic review	To determine the magnitude of risk reduction achieved by smoking cessation in patients with CHD	12,603 smokers (20% women); duration of follow-up = 10—26 years; primary outcome = total mortality rate for each group; secondary outcomes = any further CV event (fatal or Mornon-fatal), CHD, MI or stroke	Abstinence rate: 44.9%. Ex-smokers vs. continued smokers: Mortality RR 0.64 (95% CI 0.58 to 0.71); non-fatal myocardial reinfarction, RR 0.68 (95% CI 0.57 to 0.82)	Quitting smoking is associated with a substantial reduction in risk of all-cause mortality among patients with CHD
van den Berg et al., 2019 [31]; Netherlands	Observational cohort study	To quantify the relationship between smoking cessation after a first CV event and the risk of recurrent CV events and mortality	4673 (29.5% women); duration of follow-up = 7.4 years; Cox models used to quantify relationship between smoking status and risk of MACE (stroke, MI, vascular mortality and mortality)	Risk of recurrent MACE: quit smoking after CV event vs. continued smoking after CV event, HR[b] = 0.71 (95% CI 0.60 to 0.84); ex-smokers vs. continued smoking after CV event, HR[b] = 0.66 (95% CI 0.49 to 0.88); never smoked vs. continued smoking after CV event, HR[b] = 0.51 (95% CI 0.44 to 0.60)	Cessation of cigarette smoking after a first cardiovascular event is related to a substantial lower risk of recurrent vascular events
Steele et al., 2017 [48]; UK	Retrospective cohort study	To examine the association between smoking status and 1-year mortality in patients with STEMI managed by primary PCI	1796 (27.3% women): 47.1% smokers; 26.5% ex-smokers; 23.2% who had never smoked	Ex-smokers vs. never smoked, HR 1.08 (95% CI 0.66 to 1.77); current smokers vs. never smoked, HR 1.47 (95% CI 0.90 to 2.39); female sex, HR 1.08 (95% CI 0.74 to 1.59)	No evidence of an association between mortality and smoking status in patients with acute STEMI
Wilson et al., 2000 [49]; Canada	Meta-analysis	To determine the effect of smoking cessation on mortality after MI	12 studies and 5878 patients; data from six countries; publications from 1966 to 1996 in MEDLINE and EMBASE; duration of follow-up = 2—10 years	Ex-smokers vs. continued to smoke, OR 0.54 (95% CI 0.46 to 0.62); in women, ex-smokers vs. continued to smoke, OR 0.36 (95% CI 0.23 to 0.54); in men, ex-smokers vs. continued to smoke, OR 0.52 (95% CI 0.45 to 0.58)	Smoking cessation is associated with reduced mortality after MI in women

Serrano et al., 2003 [50]; Spain	Case-control (1:1) study	To estimate the association between the risk of occurrence of fatal or non-fatal reinfarction in patients who continue to smoke or stop smoking after a first infarction and are treated with secondary prevention measures	985 coronary patients (aged < 76 years); survived > 6 months after the first AMI	New AMI: continued to smoke vs. never smoked, OR 2.80 (95% CI 1.35 to 5.80); ex-smokers vs. never smoked, OR 0.90 (95% CI 0.47 to 1.71); continued to smoke vs. ex-smokers, OR 2.90 (95% CI 1.35 to 6.20)	The risk of reinfarction in patients who stop smoking is similar to the risk of non-smokers before the first infarction; the risk of reinfarction is three times higher in patients who continue to smoke after an acute coronary event compared with patients who quit
Rakowski et al., 2012 [51]; Poland	Retrospective cohort study	To evaluate the influence of smoking on outcome in patients with STEMI treated with primary PCI	1086 patients with MI (23.6% women). Current smokers: current smokers or former smokers who stopped smoking < 30 days before the event. Non-smokers: never smoked or former smokers who stopped smoking > 30 days before the event	Current smokers vs. non-smokers[b]. Ischaemic complications at 30 days: death, OR 0.71 (95% CI 0.32 to 1.54); death + reinfarction, 0.81 (95% CI 0.42 to 1.59). Ischaemic complications at 1 year: death, OR 0.71 (95% CI 0.37 to 1.36)	No evidence of an association between mortality and smoking status in patients with acute STEMI, but this result may be explained by differences in baseline characteristics or classification of smoking status
Rallidis et al., 2008 [52]; Greece	Observational cohort study	To evaluate the impact of smoking habits on long-term outcome in individuals who sustained an AMI aged ≤ 35 years	135 patients (14.8% women); duration of follow-up = 10 years; clinical endpoints = readmission for ACS, cardiac death or coronary revascularization because of clinical deterioration	Smoking rate, 94.8%; after AMI, 55.6% continued to smoke; 44 (32.6%) patients presented cardiac events (three cardiac deaths, 30 ACSs, 11 revascularizations); continued to smoke vs. ex-smokers, RR 2.35 (95% CI 1.5 to 5.25)	Persistence of smoking is the most powerful predictor for the recurrence of cardiac events in patients with premature AMI (aged ≤ 35 years).
Epstein et al., 2017 [53]; UK	Observational cohort study	To assess whether smoking cessation after an ischaemic stroke or TIA improves outcomes compared with continued smoking	1072 patients without diabetes (34% women); duration of follow-up = 4.8 years; primary outcome = recurrent stroke, MI or death	Abstinence rate, 42.0%. Ex-smokers vs. continued to smoke: stroke, RR 0.68 (95% CI 0.44 to 1.05); MI, HR 0.67 (95% CI 0.35 to 1.28); death, HR 0.47 (95% CI 0.29 to 0.76); stroke, MI or death, HR 0.66 (95% CI 0.48 to 0.90)	Cessation of cigarette smoking after an ischaemic stroke or TIA was associated with significant health benefits over 4.8 years in the Insulin Resistance Intervention After Stroke (IRIS) trial cohort

ACS: acute coronary syndrome; AMI: acute myocardial infarction; CHD: coronary heart disease; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MACE: major atherosclerotic cardiovascular events; MI: myocardial infarction; OR, odds ratio; PCI: percutaneous coronary intervention; RR: relative risk; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischaemic attack.

[a] Women were not analysed separately, except for one article.

[b] Adjusted for age and sex.

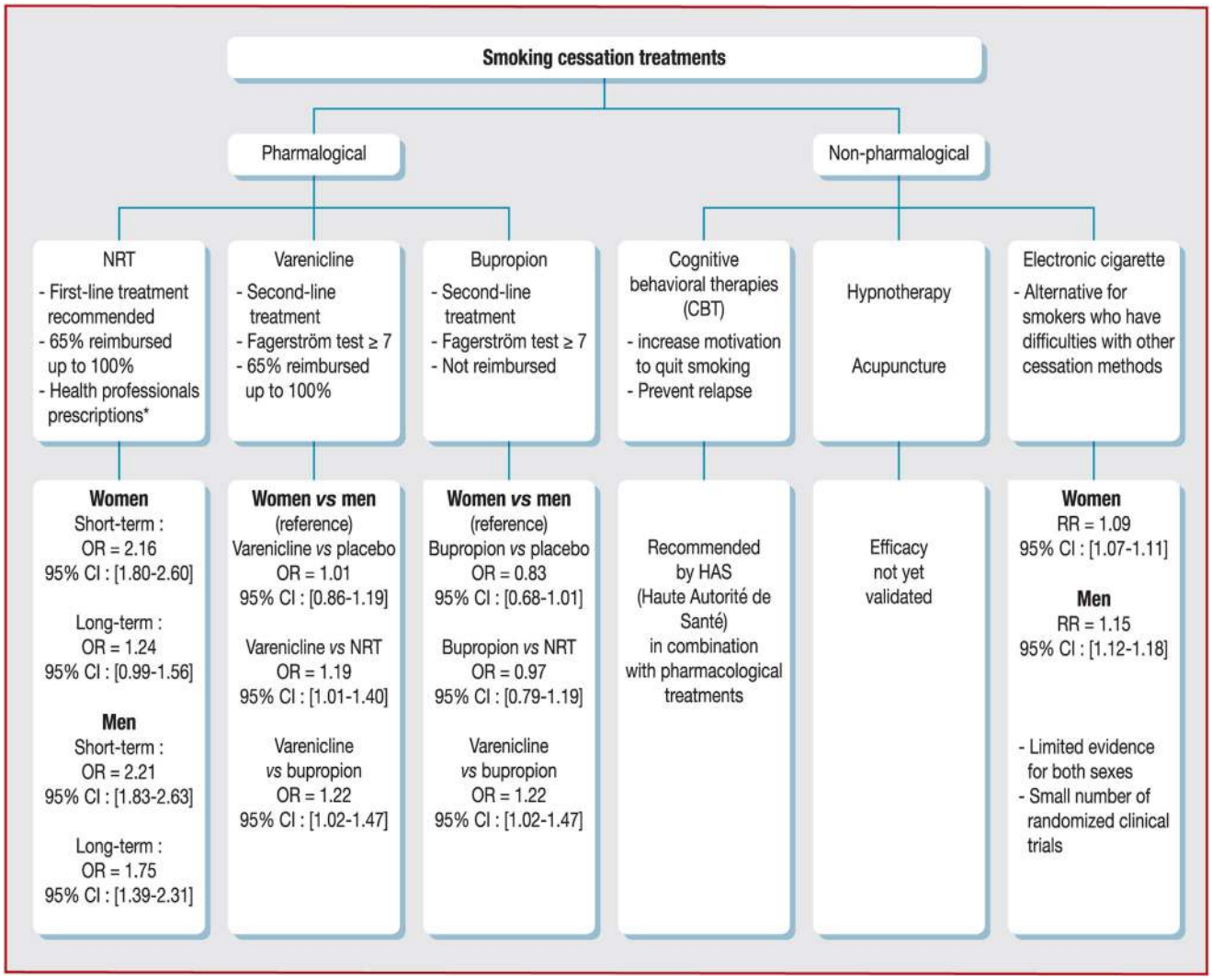

Figure 3. Smoking cessation treatment recommendations in France, and level of efficacy in women compared with men [42—45]. CI: confidence interval; HAS: Haute Autorité de Santé; NRT: nicotine replacement therapy; OR: odds ratio; RR: relative risk.[a] Preventive doctors and nurses, occupational physicians and nurses, midwives, dental surgeons, nurses and physiotherapists.

hormone contraception increase the enzymatic metabolism of nicotine and its metabolite cotinine, through stimulation of cytochrome P450 2A6 [26].

''Smoker's paradox'' in women

''Smoker's paradox'' is sometimes reported, as a counter-intuitive association between smoking status and improved short-term outcomes in various cardiovascular disease states, including reperfused ST-segment elevation MI [27]. However, no specific studies have addressed the smoking paradox in women. Yet, among 3133 patients with ST-segment elevation MI followed in a UK cardiothoracic centre over a 3-year period, smoking status had no significant effect on survival, potentially because of the modest number ($n = 723$) of female patients in the study, and overall survival did not differ between sexes ($P = 0.72$) [28]. Finally, smokers with acute MI are often younger and have fewer cardiovascular risk factors than non-smokers, suggesting that some of the crude association between smoking and improved outcomes is attributable to confounding.

Smoking cessation in women

Cardiovascular benefits of smoking cessation

Smoking cessation is recommended for both primary and secondary prevention, regardless of age and sex, and is the most effective prevention strategy compared with other preventive strategies [29]. In secondary prevention, in patients aged ≤ 45 years with acute or stable obstructive coronary artery disease, pursuit of active smoking has the strongest impact on prognosis (adjusted hazard ratio 2.70, 95% CI 2.05 to 3.55) [30]. Smoking cessation is particularly beneficial for women smokers who have had a stroke or an MI, regardless of the number of years of tobacco exposure (Table 1). Smoking cessation reduces the risk of recurrence cardiovascular event (stroke, MI or cardiovascular death) by 34% after a first stroke or MI. In addition, smoking cessation reduces the risk of recurrence of premature MI by up to 50% [31]. Therefore, women who smoke should have the support of a healthcare professional to ensure successful and sustained cessation.

Table 2 Efficacy and safety of smoking cessation methods after stroke or myocardial infarction[a].

Reference; country	Type of study	Objective	Patients	Intervention; follow-up; outcomes	Effectiveness results	Safety results
Parikh et al., 2020 [54]; USA	Systematic review	To evaluate the evidence for efficacy and safety of smoking-cessation pharmacotherapy in patients with stroke and TIA	Eight studies (three included ischaemic stroke and TIA, two included SAH and three did not specify)	Pharmacotherapy (varenicline, bupropion or NRT); individual counselling session; free NRT	Behavioural interventions combined with smoking cessation therapies resulted in numerically higher but non-significant cessation rates	NRT versus counselling + NRT was associated with more seizures (9% vs. 2%; $P = 0.024$) and delirium (19% vs. 7%; $P = 0.006$)
Joseph et al., 2012 [55]; USA	Systematic review	To identify and discuss the best approaches to assist smoking cessation among patients with CVD	Patients with CVD	Behavioural therapy (intensity counselling); brief behavioural therapy (as short as 3 minutes); combination therapy (NRT and bupropion)	Behavioural therapy (intensity counselling), OR 2.3 (95% CI 2.0 to 2.7); brief behavioural therapy, OR 1.3 (95% CI 1.01 to 1.6)	NRT patch: skin reactions, sleep disturbance; NRT gum: mouth soreness, hiccups, dyspepsia, jaw ache; NRT inhaler: mouth/throat irritation, coughing, rhinitis; NRT nasal spray: nasal congestion; bupropion[b]: insomnia, dry mouth
Rigotti et al., 2010 [56]; USA	Multicentre, double-blind, randomized trial	To evaluate the efficacy and safety of varenicline in smokers with CVD	714 smokers with CVD (16.5% women); 353 received varenicline and 350 received placebo	Varenicline or placebo (1 mg twice daily); smoking-cessation counselling for 12 weeks; follow-up = 52 weeks; primary endpoint = CO-confirmed ($\leq$ 10 ppm) continuous abstinence rate from weeks 9—12 (last 4 weeks of treatment)	Continuous abstinence rate from weeks 9—12: varenicline 47.0% vs. placebo 13.9% (OR 6.11, 95% CI 4.18 to 8.93); continuous abstinence rate from 9—52 weeks: varenicline 19.2% vs. placebo 7.2% (OR 3.14 95% CI 1.93 to 5.11); CV mortality rate, OR—0.3% (95% CI—1.3 to 0.7); all mortality rate, OR—0.3 (95% CI—2.3 to 0.6); CV event, OR 1.4% (95% CI—2.3 to 5.0); serious adverse events, OR 0.5% (95% CI—3.1 to 4.1)	Varenicline is effective for smoking cessation in smokers with CVD; it was well tolerated and did not increase CV events or mortality

Table 2 (*Suite*)

Reference; country	Type of study	Objective	Patients	Intervention; follow-up; outcomes	Effectiveness results	Safety results
Planer et al., 2011 [57]; Israel	Randomized trial	To examine safety and efficacy in patients with ACS	149 patients (20.5% women)	Bupropion or placebo for 8 weeks, and counselling (nurse-led, hospital- and telephone-based support)	Abstinence at 3 months: bupropion 45.0% vs. placebo 44.0% ($P = 0.99$); abstinence at 3 months: bupropion 37.0% vs. placebo 42.0% ($P = 0.61$); abstinence at 1 year: bupropion 31.0% vs. placebo 43.0% ($P = 0.86$); safety outcome at 1 year: bupropion vs. placebo, OR 0.23 (95% CI 0.07 to 0.78)	Bupropion is not effective for smoking cessation after ACS; no significant adverse effects found
Eisenberg et al., 2013 [58]; Canada	Multicentre randomized trial	To examine smoking cessation rates in smokers with AMI, to determine whether bupropion, started in-hospital, is safe and can improve cessation rates at 1 year	392 smokers (16.5% women); 192 received bupropion and 200 received placebo	Bupropion or placebo (150 mg daily for 3 days, followed by 150 mg twice daily for the remainder of the 9-week treatment period) and low-intensity counselling; point-prevalence abstinence was assessed by 7-day recall and biochemical validation of expired CO ($\leq$ 10 ppm)	Point abstinence rate at 12 months: bupropion 37.2% vs. placebo 32.0% ($P = 0.33$); continuous abstinence rate at 12 months: bupropion 26.8% vs. placebo 22.2% ($P = 0.34$); MACE rates were similar (13.0% vs. 11.0%, respectively; $P = 0.64$)	Bupropion is not effective for smoking cessation after AMI; no significant adverse effects found

ACS: acute coronary syndrome; AMI: acute myocardial infarction; CO: carbon monoxide; CV: cardiovascular; CVD: cardiovascular disease; MACE: major adverse cardiac events; NRT: nicotine replacement therapy; SAH: subarachnoid haemorrhage; TIA: transient ischaemic attack.

[a] Women were not analysed separately.

[b] Contraindications for bupropion: history of seizure disorder, bulimia, anorexia nervosa, current use of bupropion, allergy to bupropion, use of monoamine oxidase inhibitor in past 14 days, pregnancy or breast feeding. Risk factors that lower the seizure threshold should be considered relative contraindications, e.g. central nervous system tumour, history of stroke or closed head trauma, brain surgery, abrupt withdrawal from alcohol or benzodiazepines and medications that lower the seizure threshold (antipsychotics, antidepressants, antimalarials, theophylline, systemic corticosteroids, tramadol, quinolones, sedating antihistamines and opioids)

Inequality between men and women in smoking cessation

Although quitting smoking may be difficult for women, medications can be an effective aid to smoking cessation [32]. In secondary prevention, in a meta-analysis of more than 20,000 patients with coronary heart disease, the rate of smoking cessation failure or persistence was equivalent in both sexes [33]. Nevertheless, in the long term, women had more difficulty than men in maintaining abstinence, which can be hindered by psychological factors as well as the fear of weight gain [34].

Treatment approaches to smoking cessation

In France, pharmacological and non-pharmacological methods are available to quit smoking (Fig. 3). In patients with CVD, only varenicline has been shown to be effective to date, with a 6-fold greater efficacy than placebo (Table 2). The American College of Cardiology recommends varenicline or nicotine replacement therapy in combination for patients with stable outpatient CVD, as well as in patients after an acute coronary syndrome [35]. Recent recommendations from the American Thoracic Society highlight the preferential use of varenicline, including in smokers who are unwilling to quit [36].

A new contribution to this work is the updated synthesis on tobacco user evolution (manufactured cigarettes, rolled tobacco, shisha) in women, and their cardiovascular risk. We have also reported recent findings on the hot topic of cardiovascular risk of electronic cigarette use in women. In fact, women receive less smoking cessation counselling after an acute MI compared with men [37]. There is a paucity of literature concerning smoking cessation management for women, despite growing evidence of the increased risk of CVD as a result of tobacco consumption among women. To our knowledge, the Women's Initiative for Non-smoking (WINS) was the unique initiative in the literature [38].

Conclusions

Despite a favourable trend in recent years in the French population, the prevalence of smoking among women remains worrisome, particularly among those aged > 55 years. Female smokers are particularly exposed to the risk of heart attack and stroke before the age of 65 years. Smoking cessation reduces cardiovascular risk in women smokers, regardless of the number of years of exposure, in both primary and secondary prevention. In women, pharmacological and non-pharmacological smoking cessation strategies have been shown to be effective in reducing cardiovascular risk. Further studies are needed to clarify the cardiovascular impact of electronic cigarette use and its effectiveness in terms of long-term smoking cessation. Educating healthcare professionals about the risk of stroke and heart attack in female smokers, especially those on oestrogen-progestin therapy, is a key issue in reducing the cardiovascular consequences of tobacco use.

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