



Clinical update

Managing tobacco use: the neglected cardiovascular disease risk factor

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Cigarette smoking is a major risk factor for cardiovascular disease (CVD) and the leading avoidable cause of death worldwide. Exposure to secondhand smoke (SHS) increases the risk of CVD among non-smokers. Smoking cessation benefits all smokers, regardless of age or amount smoked. The excess risk of CVD is rapidly reversible, and stopping smoking after a myocardial infarction reduces an individual's risk of CVD mortality by 36% over 2 years. Smoking cessation is a key component of primary and secondary CVD prevention strategies, but tobacco use often receives less attention from cardiologists than other risk factors, despite the availability of proven treatments that improve smoking cessation rates. Both psychosocial counselling and pharmacotherapy are effective methods to help smokers quit, but they are most effective when used together. The first-line medications licensed to aid smoking cessation, nicotine replacement therapy, bupropion and varenicline, are effective in and appropriate for patients with CVD. An evidence-based approach for physicians is to routinely ask all patients about smoking status and SHS exposure, advise all smokers to quit and all patients to adopt smoke-free policies for their home and car, and offer all smokers in the office or hospital brief counselling, smoking cessation pharmacotherapy, and referral to local programmes where psychosocial support can be sustained in person or by telephone. Like other chronic diseases, tobacco use requires a long-term management strategy. It deserves to be managed as intensively as other CVD risk factors.

Keywords

Tobacco use • Cigarette smoking • Secondhand smoke exposure • Cardiovascular disease • Coronary heart disease • Prevention • Treatment

Introduction

Tobacco use is the leading preventable cause of death worldwide, responsible for >5 million deaths annually, or 12% of all deaths.¹ Cardiovascular disease (CVD) causes 29% of tobacco-attributable deaths.² Approximately one-half of regular smokers will die of a tobacco-related disease, losing on average 10 years of life compared with never smokers.^{3,4} The proportion of deaths due to tobacco is larger in high-income countries, where it is 18% and exceeds the proportion of deaths attributed to high blood pressure (17%) or to overweight and obesity (8.4%).⁵ Globally, the toll of tobacco-attributable mortality is rising and the burden is shifting from high-income to low- and middle-income countries. By 2030, tobacco use is expected to account for >8 million deaths annually.⁵

More than half of the decline in CVD mortality over the past half century was attributed to reductions in major CVD risk factors

including tobacco use.⁶ During this time, the prevalence of cigarette smoking decreased substantially in North America and Europe, but the decline has slowed in the past decade.^{7,8} In 2011, 19% of US adults (21.6% of men, 16.5% of women) smoked cigarettes.⁷ Smoking prevalence among European countries varies but is generally higher than in the USA.² A substantial proportion of individuals continue to smoke even after they develop CVD. In Europe, the smoking prevalence of individuals who have experienced a cardiovascular event was 20.3% in 1995, 21.2% in 1999–2000, and 18.2% in 2006–07.⁹

Reducing tobacco use is a central goal of primary and secondary prevention strategies for CVD.^{6,10} In the practice of clinical cardiology, however, tobacco use is often the neglected CVD risk factor, receiving far less attention than hypertension, hyperlipidaemia, or diabetes. This is not consistent with delivering evidence-based high-quality care. Effective smoking cessation treatments

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exist, and cardiologists have the responsibility to use these treatments as actively as they treat other CVD risk factors. This review will summarize the evidence base for treating tobacco users and outline a strategy that can be implemented in clinical practice. The review focuses on cigarettes because they are the most common form of tobacco used worldwide and because the bulk of evidence about treatment derives from studies in cigarette smokers. Information about other forms of smoked and smokeless tobacco products, including snus and electronic cigarettes, are available elsewhere.^{11,12}

Cardiovascular risks of cigarette smoking and exposure to secondhand smoke

Tobacco use is a well-established risk factor for CVD incidence and mortality.^{3,13} Smoking increases an individual's risk of death from all vascular diseases two- to three-fold³ (Figure 1). Worldwide, 10–30% of all CVD deaths are attributable to tobacco.^{1,14} Among men aged 30–44 years, however, 48% of cardiovascular deaths are attributable to tobacco use.¹ Smokers' excess risk of CVD increases with number of cigarettes smoked daily, but exists even for smokers of one to five cigarettes per day.¹⁴ Few data exist about occasional (non-daily) smoking, but in one study men but not women who smoked cigarettes occasionally had an increased risk of total and cardiovascular mortality.¹⁵

Cigarette smoking has been specifically identified as a cause of coronary heart disease (CHD) [including myocardial infarction (MI) and sudden death], cerebrovascular disease (stroke), peripheral artery disease (PAD), and abdominal aortic aneurysm.^{16–18} Smokers risk of heart failure is twice the risk of non-smokers, and smokers with heart failure have a worse prognosis than non-smokers with heart

failure.¹⁹ Smoking can also induce and worsen serious cardiac arrhythmias by many mechanisms.²⁰

Among individuals with established CVD, smoking reduces the success of treatments. Smokers who undergo percutaneous coronary interventions (PCIs) or coronary artery bypass graft surgery are at increased risk of myocardial re-infarctions and death compared with non-smokers.^{21,22} Current smoking is an independent predictor of long-term stent thrombosis after PCIs.²³ Cigarette smoking also influences the efficacy of antiplatelet therapies. It is correlated with aspirin resistance, probably due to its stimulating effect on platelet aggregation.²⁴ Cigarette smoking (but not nicotine alone) induces the cytochrome P450 1A2 (CYP1A2), which is involved in the metabolism of clopidogrel. This results in greater inhibition of platelet aggregation in smokers compared with non-smokers.²⁵ This finding is corroborated by a study suggesting that clopidogrel is effective in smokers with CVD to preventing all-cause and cardiovascular mortality but not in non-smokers or former smokers.²⁶ Newer antiplatelet therapies (prasugrel, ticagrelor, and ticlopidine) do not seem to be influenced by smoking.

The cardiovascular risk of tobacco use is not limited to smokers. Non-smokers who are regularly exposed to other people's tobacco smoke also have an increased risk of CVD. Exposure to secondhand smoke (SHS) increases the risk of CHD morbidity and mortality by 25–30% among non-smokers.²⁷ Globally, CVD is responsible for >87% of the estimated 430 000 adult deaths caused by SHS.²⁸ The risk is rapidly reversible, as shown in multiple studies documenting a rapid decline in hospital admissions for MI after the adoption of smoking bans.²⁹ In a meta-analysis of 11 studies assessing the cardiovascular benefits of bans on smoking in public places, there was an overall 17% decreased risk of acute MI after implementation of smoking bans in public places.²⁹ A Cochrane review has also shown a consistent reduction in hospital admissions for cardiac events after smoking bans have been implemented.³⁰

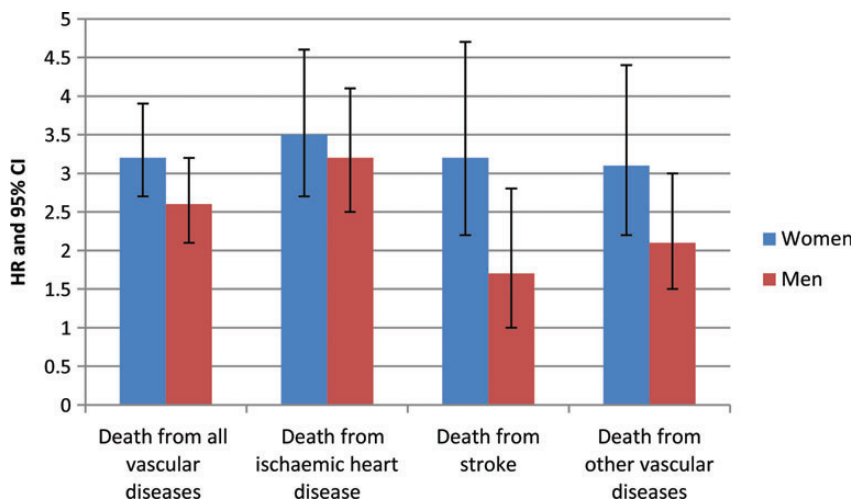


Figure 1 Cardiovascular mortality for current smokers compared to never smokers (hazard ratios were adjusted for age, educational level, alcohol consumption, and body-mass index. Adapted from Jha *et al.*³). HR, hazard ratios; CI, confidence intervals.

Pathophysiology of cardiovascular disease risk

Cigarette smoking has multiple adverse effects on the cardiovascular system that promote atherogenesis and trigger acute cardiovascular events. Cigarette smoke induces CVD through endothelial injury, formation of atheroma and a superimposed prothrombotic influence.³¹ The effects of cigarette smoking on CVD are mediated through three principal constituents: nicotine, carbon monoxide (CO), and oxidant gases. (Figure 2) Other authors have described in details the biochemical mechanisms of nicotine on the cardiovascular system,^{31,32} we will here summarize the main mechanisms.

Nicotine binds to nicotinic cholinergic receptors in the brain and acts as a sympathomimetic agent.³³ It stimulates the release of catecholamines, leading to increases in heart rate, blood pressure, and myocardial contractility that increase myocardial work and oxygen demand.³⁴ Nicotine also induces vasoconstriction through its action on alpha-adrenergic receptors and by inducing endothelial dysfunction.^{31,35} This results in a reduced coronary and cerebral blood flow.

Carbon monoxide is produced by combustion and is found in cigarette smoke. It binds more avidly than oxygen to haemoglobin and decreases oxygen supply to organs in the body. It results in relative hypoxaemia that can precipitate ischaemic events. In addition, in

response to hypoxaemia, red blood cell mass increases and lead to hyperviscosity, which contributes to hypercoagulation in smokers.³²

Cigarette smoke contains high levels of oxidant gases such as oxides of nitrogen and free radicals. These induce inflammation, endothelial dysfunction, and oxidation of lipids, which are mediators in the pathogenesis of CVD. They also contribute to platelet activation, thrombogenesis,³⁶ and enhance coagulability through increase in plasma fibrinogen.³⁷ Other components of cigarette smoke, such as metals and polycyclic aromatic hydrocarbons, also damage endothelial cells and contribute to atherosclerosis.

The increase in risk of CVD associated with smoking is also mediated though other cardiovascular risk factors such as an increase in low-density lipoprotein-cholesterol and triglyceride, a decrease in high-density lipoprotein cholesterol, an increased risk of type 2 diabetes, and possibly an increase in blood pressure.^{38–40}

Health benefits of smoking cessation: a rapid reduction in cardiovascular disease risk

Smoking cessation benefits virtually all smokers, regardless of the duration or intensity of their smoking, degree of illness, or age at quitting.^{13,41} Smoking cessation early in life is particularly beneficial.³

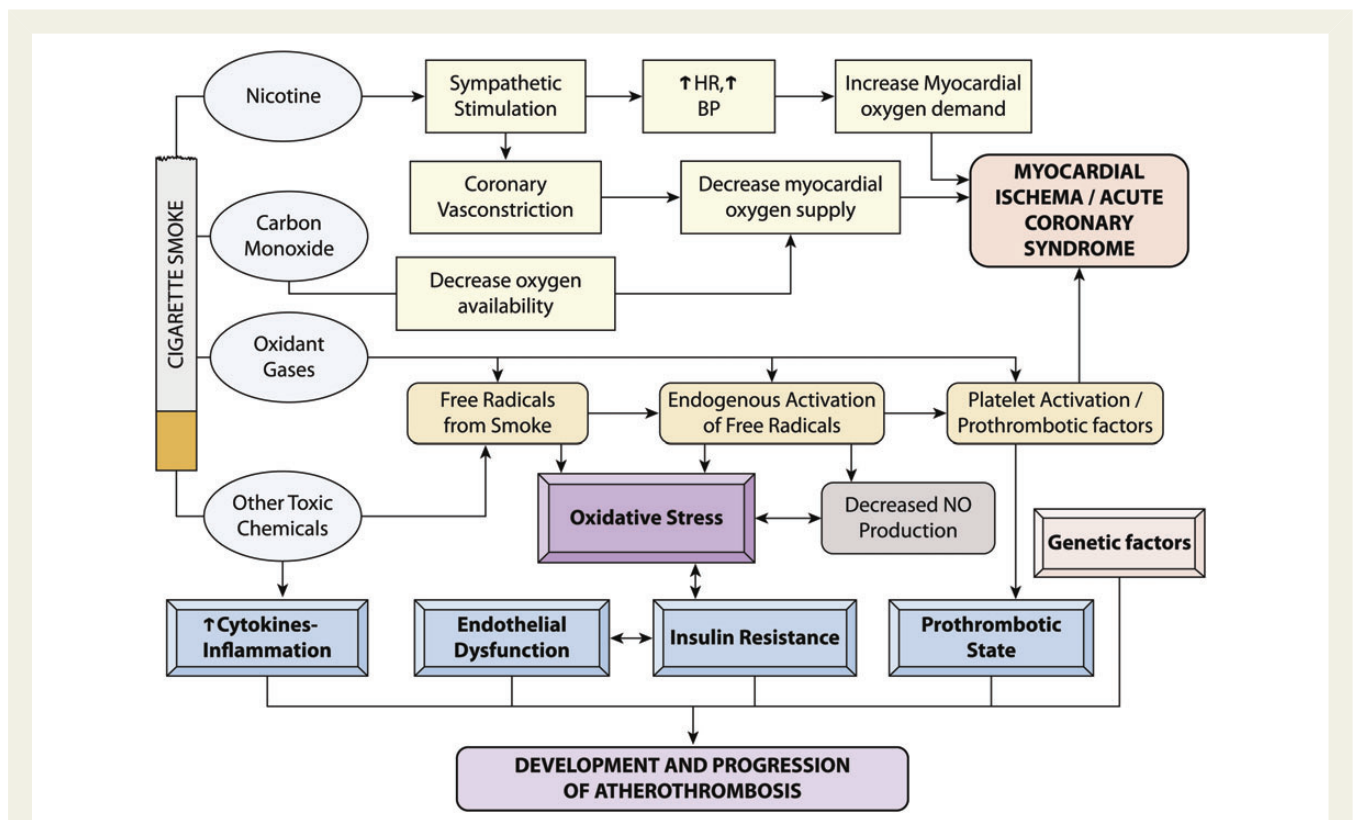


Figure 2 Pathophysiological effect of cigarette smoking and nicotine on cardiovascular disease. HR, heart rate; BP, blood pressure; NO, nitrogen monoxide. Figure reprinted with permission from Salahuddin S, Prabhakaran D, Roy A. Pathophysiological mechanisms of tobacco-related CVD. *Global Heart*. 2012;7(2):113–119.

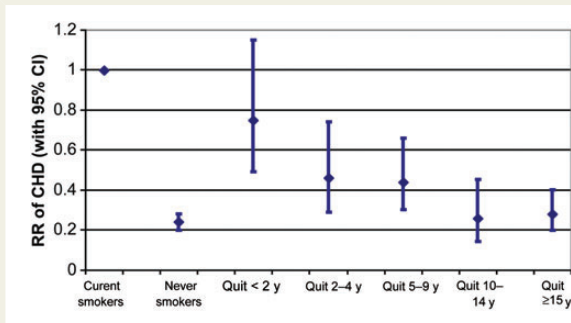


Figure 3 Benefits of quitting smoking on the incidence of coronary heart disease. RR, risk ratio; CHD, coronary heart disease; CI, confidence interval; y, years. Figure adapted from Kawachi et al.⁴³

Stopping smoking before the age of 40 years reduces the risk of tobacco-attributable death by 90%,³ but quitting at any age reduces mortality rates.¹³

Quitting smoking reduces smokers' risk of MI and stroke, and smokers' excess risk of CVD is rapidly reversible after smoking cessation.⁴² Nearly, half of the excess CHD risk is eliminated within 2 years of quitting⁴³ (Figure 3). The risk of stroke is approximately the same as a non-smoker 5 years after quitting smoking.⁴⁴ Among smokers with PAD, cessation decreases the 5-year risk of amputation by 10 times and decreases mortality by 50%.⁴⁵ Among smokers with CHF, smoking cessation decreases mortality by 30% within 1 year after cessation.¹⁹ Rapid improvements in endothelial function and hypercoagulability among smokers who quit may underlie these epidemiological observations.⁴⁶

Stopping smoking after acute coronary syndrome (ACS) or MI is one of the most effective actions for secondary prevention of CVD. A significant morbidity reduction has been observed within 6 months after an ACS among smokers who quit, compared with those who do not.⁴⁷ Smokers who quit after an MI have a 36% reduction in CVD mortality over 2 years compared with continuing smokers.⁴⁸

Stopping smoking also improves clinical outcomes after CABG surgery or PCIs. Smokers who quit after CABG, compared with those who continue to smoke, improve their survival and reduce their risk of additional procedures.⁴⁹ Stopping smoking after a PCI decreases a smoker's excess risk of death compared with individuals who continue to smoke.^{21,50}

Challenges to success in smoking cessation

Surveys of US adults consistently report that ~70% of smokers want to quit smoking and more than half tried to do so in the past year, but only 6% of those who attempted to quit succeeded.⁵¹ One reason for the low success rate is that few smokers use any tobacco cessation treatment when attempting to quit. Only one-third of US smokers making a quit attempt seek assistance.⁵² Even in the UK, which has a national system of tobacco treatment and coverage for medications, only half of smokers who made a quit attempt in 2011 used a

cessation aid.⁵³ Smoking cessation rates in the population could be improved if more smokers used evidence-based treatment when they tried to quit. The healthcare delivery system is a key channel for accomplishing this goal. Physicians and other clinicians have a unique opportunity to extend the reach of treatment to more smokers and a responsibility to do so.

A major barrier to smoking cessation success is the addictive nature of nicotine. Inhaling cigarette smoke rapidly delivers nicotine to the brain, where it binds to nicotinic cholinergic receptors, leading to a release of dopamine and other neurotransmitters that reinforce smoking and the activities associated with smoking. Repeated smoke exposure up-regulates nicotine receptors, produces tolerance to higher doses of nicotine, and generates withdrawal symptoms when nicotine levels fall.³³ These symptoms include craving for cigarettes, irritability, anger, restlessness, anxiety, depressed mood, difficulty concentrating, insomnia, and increased hunger. They appear a few hours after the last cigarette is smoked, peak within 48–72 h and gradually wane to pre-cessation levels after 2–4 weeks, although cravings often continue.⁵⁴

Smoking is also maintained by conditioned cues or stimuli whose appearance triggers cigarette cravings. To stop smoking, therefore, a smoker must manage pharmacological nicotine withdrawal and extinguish the learned behavioural associations with smoking. This dual challenge leads many individual quit attempts to fail. Most smokers need several quit attempts before being successful for the long term. Factors associated with a less success in quitting include a high level of nicotine dependence, less education, comorbid psychiatric illness, other substance use, co-habitation with another smoker, less social support for quitting, and low self-confidence in the ability to quit. Individuals with these conditions can quit but often require more intensive or prolonged treatment.

Smoking cessation treatment

Evidence from randomized controlled trials has clearly identified psychosocial support (i.e. counselling) and pharmacotherapy as two categories of effective smoking cessation treatment.^{41,55–59} Psychosocial support enhances motivation to quit smoking and builds coping skills to avoid relapse, while pharmacotherapy relieves nicotine withdrawal symptoms. Combining them produces higher quit rates than using either one alone.⁶⁰ While success increases with increasing treatment intensity, even brief advice to quit by a physician or other clinician is effective.⁴¹ Hypnosis and acupuncture have not shown long-term efficacy for smoking cessation in clinical trials.⁴¹

The traditional recommendation to smokers is to quit abruptly after a short period of preparation.⁴¹ However, evidence suggests that gradually reducing cigarette intake with the clear goal of future quitting may produce comparable success.⁶¹ Far less evidence is available to guide smokers who are not ready to make a quit attempt, although motivational interviewing counselling techniques appear to be useful.⁶²

The relapsing pattern of tobacco use among smokers who try to quit has led to framing tobacco use as a chronic condition or chronic disease.⁴¹ This has implications for treatment. Successful treatment of other chronic diseases like diabetes, hypertension, and CVD require a long-term management strategy, and smoking requires the same approach.⁶³

Smoking cessation counselling

Among smokers with CHD, psychosocial interventions for smoking cessation increase 1-year smoking abstinence rates (OR: 1.66, 95% CI: 1.25 to 2.22) according to a meta-analysis of 16 randomized controlled trials.⁶⁴ These interventions use cognitive-behavioural therapy methods.

Psychosocial methods were initially designed for in-person delivery to individuals or groups, but to reach more smokers, the techniques have been adapted for delivery by telephone (voice and text messaging), on the web, and via social media.⁶⁵ Strong evidence supports the efficacy of delivering smoking cessation counselling as a series of proactive (i.e. counsellor-initiated) telephone calls; so-called 'quitlines' exist in many countries.⁶⁶ Text messaging is also effective for smoking cessation.⁶⁷ There is as yet less evidence to demonstrate the efficacy of web-based programmes and no data on smart phone applications.

Pharmacotherapy

Strong evidence supports the efficacy of three medications to help smokers quit. They are nicotine replacement products, bupropion, and varenicline. They are ranked as equivalent first-line treatment choices in US clinical practice guidelines and further described below⁴¹ (Table 1).

Of these three medications, bupropion is the only one to have potential interactions with major drug classes used in cardiology. Bupropion is mainly metabolized by the cytochrome P450 2B6 and concomitant use of drugs acting on this isoenzyme (mainly clopidogrel in cardiology) can increase the blood levels and effects of bupropion.

Nortriptyline, a tricyclic antidepressant, and clonidine, an antihypertensive agent, have also demonstrated efficacy for smoking cessation but their evidence base is smaller and they are ranked as second-line treatments in the US guidelines.⁴¹ Cytisine, a partial nicotine receptor agonist with chemical similarities to varenicline, is a low-cost drug marketed in some Eastern European countries as Tabex®. It showed efficacy in a randomized controlled trial but is not currently licensed for smoking cessation in western European Union countries or North America.⁶⁸ Selective serotonin reuptake inhibitor antidepressants and anxiolytic agents have not demonstrated efficacy for smoking cessation in randomized controlled trials.⁴¹

Nicotine replacement therapy

Efficacy

Nicotine replacement therapy (NRT) reduces nicotine withdrawal symptoms to help a smoker to stop the behaviour of smoking. In a meta-analysis of over 100 trials, NRT increased smoking abstinence rates over placebo (RR: 1.60, 95% CI: 1.53–1.68).⁵⁷ Nicotine replacement therapy products are roughly equal in efficacy but have two distinct patterns of nicotine delivery. The skin patch delivers nicotine for 16–24 h with a single application but with a slow onset of action (2–3 h). In contrast, nicotine in the gum, lozenge, inhaler, mouth spray, or nasal spray has a more rapid onset (5–30 min) but a shorter duration of action. These products must be reused throughout a day to maintain stable nicotine blood levels. As randomized controlled trials demonstrate, the most effective way to use NRT is to combine the nicotine patch with a short-acting orally or nasally

absorbed product.⁶⁹ The short-acting product is used as needed to relieve cravings that arise in the presence of the NRT patch.

Surprisingly, clinical trials of the efficacy of NRT in patients with CVD had mixed results, in part because few trials have been conducted.^{70–72} The largest trial did not find a sustained efficacy over time of NRT in outpatients with stable CVD.⁷⁰ Two other studies found that NRT was superior compared with placebo but both had very short follow-up (2 and 5 weeks).^{71,72} Despite its lack of clear evidence of efficacy in the setting of CVD, NRT is considered to be effective in CVD patients based on the substantial evidence base for smokers in general.

Safety

Theoretically, nicotine's sympathomimetic effect could increase myocardial workload and adversely affect patients with CVD, especially those with unstable CHD syndromes. However, the nicotine transdermal patch is not associated with an increased cardiovascular risk in patients with stable CVD.^{70,72,73} A study that did stress tests in smokers while actively smoking and while using nicotine patches found less exercise-induced myocardial ischaemia in the nicotine patch condition than in the smoking condition.⁷⁴

Both the US Clinical Practice Guidelines and the UK Medicine and Healthcare Products Regulatory Agency endorse the use of NRT in people with stable CVD.^{41,75} Little direct evidence is available regarding the safety of NRT in patients with severe or unstable angina, ACS, or recent stroke. A case for NRT's relative safety in acute CVD or recent MI can be made from indirect evidence. First, nicotine's adverse haemodynamic effects, which increase myocardial work, depend on its rapidity of absorption, which is slower for the patch than for smoking.⁷⁵ Second, hypercoagulability and CO play a more important role than the haemodynamic effects mediated by nicotine in precipitating acute coronary events.⁷⁵ Nicotine patches lack the thrombogenic effect of cigarette smoking and do not expose the smoker to CO. Therefore, it is reasonable to consider using NRT to treat nicotine withdrawal symptoms and promote smoking cessation once an ACS event is haemodynamically stabilized if non-pharmacological interventions are not sufficient.⁷⁵

Varenicline

Efficacy

Varenicline is a selective partial agonist of the alpha4-beta2 nicotine receptor. It has a dual mechanism of action. It relieves nicotine withdrawal symptoms by stimulating nicotinic receptors and blocks the reinforcement of smoking by preventing nicotine from binding to the receptors. Compared with placebo, varenicline more than doubles quit rates over 6–12 months, according to the most recent meta-analysis (RR: 2.32, 95% CI: 2.06–2.61).⁵⁸ Varenicline was superior to bupropion in two head-to-head trials^{58,76} and was better (with borderline statistical significance) than NRT monotherapy in one open-label randomized controlled trial.⁷⁷ No study has directly compared varenicline with combination NRT.

The efficacy of varenicline in patients with stable CVD was tested in one double-blind randomized controlled trial of over 700 smokers.⁷⁸ In that trial, varenicline increased continuous tobacco abstinence at 1 year compared with placebo (OR: 3.14, 95% CI: 1.93–5.11).

Table 1 Medications that are licensed in USA or Europe as aids for smoking cessation

Medication	Efficacy in all patients (RR with 95% CI) ^a	Efficacy in CVD patients	Common adverse effects	CVD safety	Advantages	Disadvantages and warnings	Dose	Duration (months)
Nicotine replacement therapy	1.60 (1.53–1.68)	Few randomized trials with mixed results in outpatients with CVD	Vary by NRT product	Safe in stable CVD. Weigh benefit vs. risk if recent MI (<2 week), unstable angina, ventricular arrhythmia	Often available without prescription	Vary by NRT product	Varies by product	2–6
Skin patch: 21 mg/14 mg/7 mg (for 24 h); 25 mg/15 mg/10 mg (for 16 h)	1.66 (1.53–1.81)		Skin irritation, insomnia		Easiest to use, provides steady nicotine level	Nicotine released slowly, does not allow smoker to respond to cravings	Apply 1 patch daily: 21 mg/25 mg for ≥ 10 cig/day, 14 mg/15 mg ~for <10 cig/day, taper to lower dose after 4–6 weeks	≥ 2 –3
Gum: 2 mg, 4 mg	1.43 (1.33–1.53)		Mouth irritation, jaw soreness, heartburn, hiccups, nausea		User controls nicotine dose Oral substitute for cigarettes	Proper chewing technique required, difficult to use if dental problems, no food or drink for 30 min before use and during use	1 gum every hour 4 mg for ≥ 25 cig/day 2 mg for <25 cig/day Max 24 gums/day	≥ 3
Lozenge: 1 mg/2 mg/4 mg Microtab sublingual: 2 mg	2.0 (1.63–2.45)		Hiccups, heartburn		User controls nicotine dose	No food or drink for 30 min before use and during use	1 piece every 1–2 h	3–6
Oral inhaler: 10 mg per cartridge	1.90 (1.36–2.67)		Mouth and throat irritation, cough		User controls nicotine dose Oral substitute for cigarettes	Device visible when being used	Inhale as needed Max 16 cartridges/day	3–6
Nasal spray: 10 mg/ml	2.02 (1.49–3.73)		Nasal irritation, sneezing, cough, teary eyes		User controls nicotine dose Most rapid delivery of nicotine	Local irritation to nasal mucosa (not on sale in all European countries)	Apply once to each nostril 1–2/h Max 40 applications/day	3–6
Mouth spray: 1 mg per spray dose	2.48 (1.24–4.94)		Mouth and throat irritation, hiccups, heartburn		User controls nicotine dose Oral substitute for cigarettes	Local irritation (only on sale in the UK)	1–2 sprays, up to 4 sprays per hour. Max 64 sprays per 24 h	3–6
Bupropion SR: 150 mg	1.69 (1.53–1.85)	Efficacy in randomized trial of outpatients with stable CVD (OR: 2.78, 95% CI: 1.70–4.63)	Insomnia, headache, dry mouth	Safe	Blunts post cessation weight gain while being used	Increases seizure risk, FDA boxed warning about psychiatric effects ^b	150 mg/day for 3 day then 150 mg 2 \times /day Start 1 week before quit date	3–6
Varenicline: 0.5 mg/1 mg	2.27 (2.02–2.55)	Efficacy in randomized trial of outpatients with stable CVD (OR: 3.14, 95% CI: 1.93–5.11)	Nausea, insomnia, headache	FDA advisory about potential CVD risks but absolute risk very low (<1%) ^c	Dual action: relieves nicotine withdrawal and blocks reward from smoking	FDA boxed warning about psychiatric effects ^d Reduce dose in moderate to severe renal insufficiency	0.5 mg/day for 3 days, then 0.5 mg 2 \times /day for 4 days, then 1 mg 2 \times /day Start 1 week before quit date	3–6

^aData from Cochrane reviews.^b<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/PublicHealthAdvisories/ucm169988.htm>^c<http://www.fda.gov/Drugs/DrugSafety/ucm330367.htm>^d<http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm#>

Safety

The most common side effects of varenicline are nausea, insomnia, and vivid or abnormal dreams. Varenicline was expected to have no cardiovascular risk because it does not bind to the nicotine receptor subtypes that mediate nicotine's haemodynamic effects. The large randomized trial of varenicline in patients with stable CVD observed no adverse effects on CVD events or mortality over one year.⁷⁸ Three meta-analyses that pooled safety data from multiple varenicline clinical trials have disagreed among themselves. One meta-analysis found an increased risk of serious adverse cardiovascular events associated with varenicline (Peto OR: 1.72, 95% CI: 1.09–2.71).⁷⁹ This was not found in a second meta-analysis (OR: 1.41, 95% CI: 0.82–2.42)⁸⁰ or a third one mandated by the US FDA and reported in December 2012 (adjusted hazard ratio 1.95, 95% CI: 0.79–4.82).⁸¹ In all studies, the absolute risk of serious cardiovascular events was very low (1% or less at 6–12 months). Even if present, a small risk of varenicline would likely be counterbalanced by its ability to enhance smoking cessation, which has rapid and substantial benefits on cardiovascular health.

A potential association of varenicline with behavioural changes such as hostility, agitation, depressed mood, and suicidal thoughts or actions has appeared in case reports. Interpreting them is challenging because nicotine withdrawal alone can produce these symptoms. A meta-analysis of randomized control trials of varenicline detected no increase in psychiatric illness in patients taking the drug.⁸² However, people with depression or mental illnesses were not included in these studies. Two studies of electronic health records detected no association of varenicline with psychiatric symptoms⁸³ or neuropsychiatric hospitalizations.⁸⁴ A large FDA-mandated randomized controlled trial is ongoing.⁸⁵ In the meantime, smokers started on varenicline deserve close follow-up to monitor for these symptoms.

Bupropion

Efficacy

Bupropion, an atypical antidepressant that increases dopamine and norepinephrine levels in the central nervous system, increased smoking cessation rates by 69% compared with placebo (RR: 1.69, 95% CI: 1.53–1.85) in a recent meta-analysis of randomized trials.⁵⁸ In a large trial of outpatient smokers with stable CVD, bupropion doubled the continuous abstinence rate compared with placebo.⁸⁶ However, long-term efficacy for bupropion was not observed in three trials in which bupropion was started in hospitalized smokers with acute CVD events and continued after discharge.^{87–89} These trials had relatively high smoking cessation rates in the control groups (ranging from 21 to 37%), perhaps reflecting the greater efficacy of counselling (the control condition) among smokers hospitalized with acute CVD.

Safety

The main side effects of bupropion are insomnia, headache, and dry mouth. It is contra-indicated in patients with or at risk for seizure. Studies of bupropion in patients with CVD have not shown an increase in CVD-specific adverse events compared with placebo.^{86–89}

Incorporating smoking cessation treatment into clinical practice

Physicians can influence their patients' smoking behaviour, primarily by prompting smokers to make a quit attempt. Physicians who routinely deliver brief advice to quit to all smokers increase smokers' odds of quitting by 34%.⁵⁶ Going beyond advice to provide a short counselling intervention during an office visit is more effective.

Cardiologists have a special opportunity to promote cessation. For a smoker, the diagnosis of CHD makes the health risks of smoking suddenly personally salient. Informing smokers that they have the ability to rapidly reduce the risk of future CVD events by quitting smoking is information with the potential to be highly motivating. Additionally, the cardiovascular risks of SHS exposure are not well known. Cardiologists should provide this new information by asking all patients if anyone at home smokes and advise every patient, regardless of smoking status, to adopt a smoke-free policy for the home and car.

Hospitalization is another opportunity for cardiologists to encourage smoking cessation. If the hospital is smoke-free, smokers must temporarily refrain from tobacco use. They can be encouraged to remain tobacco abstinent after discharge and start smoking cessation counselling and pharmacotherapy in the hospital. In a meta-analysis of randomized controlled trials of smokers hospitalized for a CVD diagnosis, a smoking cessation intervention started in the hospital and sustained, usually by telephone, for at least 1 month after discharge, increased smoking cessation rates by 42% (RR: 1.42, 95% CI: 1.29–1.56) 6–12 months after discharge.⁵⁵ Starting NRT in hospital increased quit rates over counselling alone.⁵⁵ In one trial of smokers hospitalized with MI, an intensive intervention of counselling and pharmacotherapy, compared with usual care, not only increased smoking cessation but also reduced all-cause mortality and hospital readmissions.⁹⁰

Guidelines for CVD prevention from the American Heart Association (2011)¹⁰ and European Society of Cardiology (2012)⁶ clearly identify smoking cessation as a key component of CVD prevention. Both the US and European Guidelines on CVD prevention clearly recommend against use of tobacco and exposure to SHS. They strongly advise that all smokers should be given advice to quit and be offered assistance that includes counselling and pharmacotherapy. The 2012 European Guidelines on CVD prevention in clinical practice include 10 'strategic steps' to guide physicians who seek to help their patients alter any behavioural cardiovascular risk factor.⁶ They provide a practical framework for addressing tobacco use in office practice.

The 2008 US Public Health Service guideline translated evidence from clinical trials into a five-step model for addressing tobacco use in office practice (5 As) (Figure 4).⁴¹ This consists of (i) systematically asking and documenting every patient's smoking status at every visit, (ii) advising all tobacco users to quit, emphasizing the personal benefits of cessation rather than the harms of continuing to smoke, (iii) assessing their intentions to quit and degree of addiction, (iv) assisting them with quitting by prescribing medication and referring to counselling resources in the community or health care system, and (v) arranging a follow-up visit. Linking smokers to telephone quitlines is standard care in countries where these are available. Referring to websites is another alternative if in-person counselling is not readily available.

An alternative, briefer three-step model for cardiac patients consists of the following: (i) Ask all patients about tobacco use and

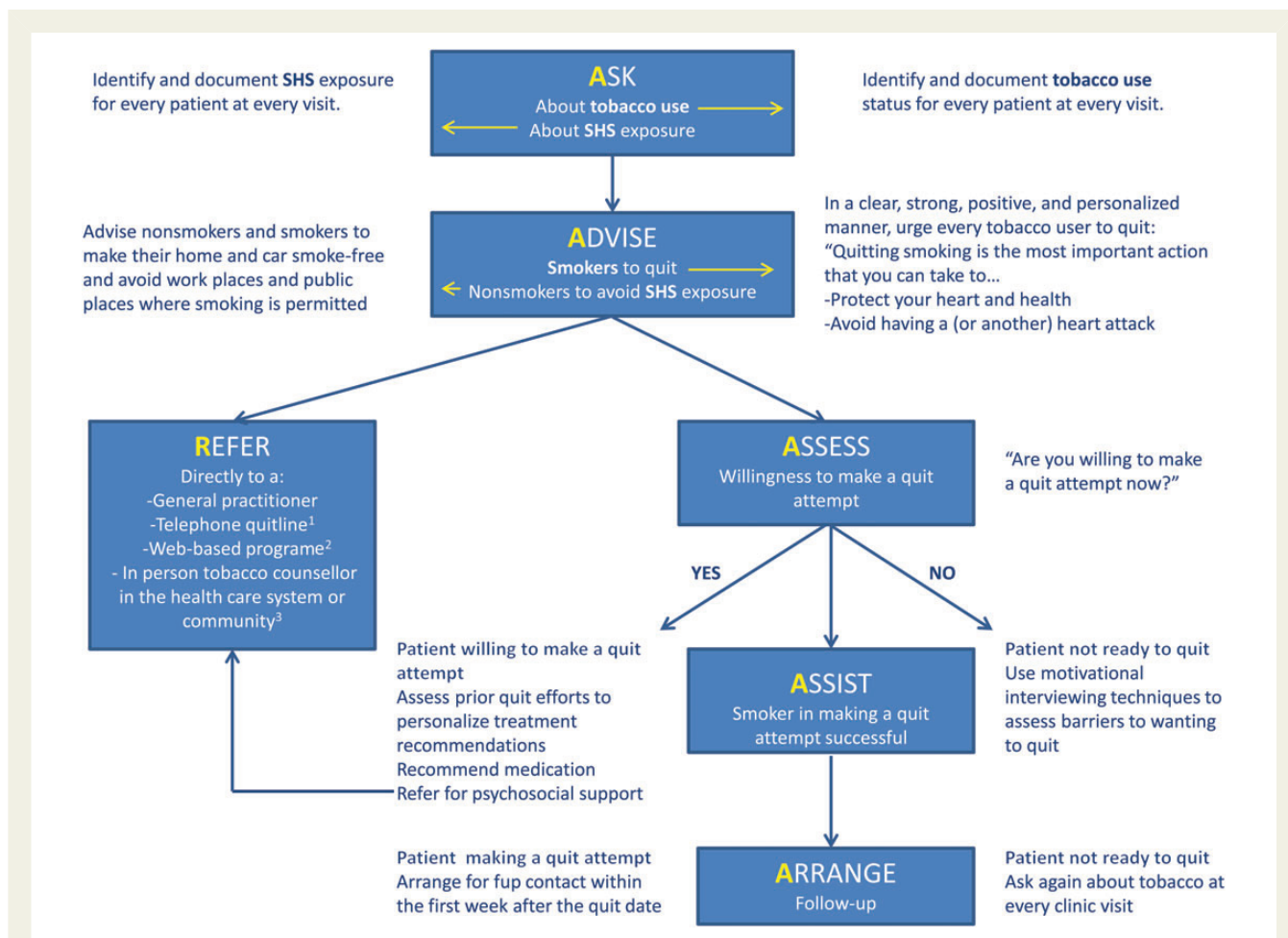


Figure 4 Alternative strategies for addressing tobacco use and secondhand smoke exposure in clinical practice. SHS, second-hand smoke; fup, follow-up. Note: adapted from 5As⁴¹, ESC guidelines⁶ and ‘Cardiology Rx for Change’⁹⁴ with modifications by the authors. ¹Quitlines: US: 800-QUIT-NOW. Map to locate quitlines elsewhere in the world: http://c.ymcdn.com/sites/naquitline.site-ym.com/resource/resmgr/GQN_Map/worldmap.swf. ² Examples of web-based programmes: becomeanex.com, quintet.com. ³ Examples of in-person programmes: NHS Stop Smoking Service (www.nhs.uk).

SHS exposure; (ii) advise all smokers to quit and all non-smokers to avoid SHS; and (iii) refer to community resources such as quitlines or websites. Prescribing pharmacotherapy to patients planning to quit is implicit but not explicit in this model (Figure 4).

Conclusions and recommendations: the cardiologist’s role

Cigarette smoking is universally recognized as a major risk factor for CVD. Smoking cessation reliably and rapidly reduces the excess risk, even among individuals who have already developed clinical CVD. A large body of evidence has demonstrated the efficacy of pharmacotherapy and psychosocial support for assisting smokers to quit and stay quit. Tobacco treatment is among the most cost-effective treatments for CVD⁹¹ and is endorsed by professional organizations of cardiologists in North America and Europe.^{6,10} Clearly, treating smoking is the standard of care for the primary and secondary prevention of CVD.

Despite this unequivocal evidence, tobacco is often the forgotten cardiac risk factor, receiving less of a cardiologist’s attention than is given to treating hypertension, hyperlipidaemia, or diabetes.⁹² This should change. Cardiologists must recognize that tobacco use has the characteristics of a chronic condition or chronic disease and deserves to be treated like one. Treating a smoker requires taking a long-term management approach that is no different from other chronic diseases. Routinely identifying smoking status, advising cessation, and referring to resources to assist smokers in making a quit attempt should be standard practice and quality measures.

Cardiologists should also communicate to all patients the newer and less well-known information about SHS exposure as a risk factor for CVD. Cardiologists should routinely ask about SHS exposure, advise all patients to adopt smoke-free policies for their homes and vehicles and recommend avoiding SHS exposure at work and in public places.

Cardiologists can also contribute as role models and advocates. As role models, cardiologists should not use tobacco products themselves. Cardiologists can advocate with their hospitals and healthcare systems to adopt smoke-free policies and make tobacco treatments

available and affordable. Cardiologists in academic settings can advocate with medical schools and training programmes to teach tobacco treatment methods to the next generation of physicians. Finally, in their communities, cardiologists can support the adoption of comprehensive tobacco control public policies that are proved to reduce tobacco use.⁹³

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N.A.R. reported having consulted without pay about smoking cessation for Pfizer and Allere Wellbeing, Inc. and having conducted research projects sponsored by Pfizer.

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