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Prevention and Treatment of Tobacco Use: *JACC* Health Promotion Series

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Abstract

Tobacco use is the leading preventable cause of death worldwide and a major risk factor for cardiovascular disease (CVD). Both prevention of smoking initiation among youth and smoking cessation among established smokers are key for reducing smoking prevalence and the associated negative health consequences. Proven tobacco cessation treatment includes pharmacotherapy and behavioral support, which are most effective when provided together. First-line medications (varenicline, bupropion, and nicotine replacement) are effective and safe for patients with CVD. Clinicians who care for patients with CVD should give as high a priority to treating tobacco use as to managing other CVD risk factors. Broader tobacco control efforts to raise tobacco taxes, adopt smoke-free laws, conduct mass media campaigns, and restrict tobacco marketing enhance clinicians' actions working with individual smokers.

Condensed abstract:

Tobacco use is the leading preventable cause of death worldwide and a major risk factor for cardiovascular disease. Both prevention of smoking initiation among youth and smoking cessation among established smokers are key for reducing smoking prevalence and the associated negative health consequences. Clinicians who care for patients with CVD should give as high a priority to treating tobacco use as they do to managing other CVD risk factors. Broader tobacco control policy efforts to raise tobacco taxes, adopt smoke-free laws, conduct mass media campaigns, and restrict tobacco marketing serve to enhance clinicians' actions working with individual smokers.

Keywords

smoking; nicotine; tobacco use disorder; smoking prevention; smoking cessation

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Introduction

Tobacco use causes over 6 million annual deaths globally and is the leading preventable cause of death worldwide (1). Over 480,000 individuals die from cigarette smoking or secondhand tobacco smoke exposure annually in the United States (2), and a smoker's life expectancy is at least 10 years shorter than a nonsmoker's (3). Each year, >150,000 U.S. adults age 35 and older die from smoking-related cardiovascular diseases (CVD) (4), making smoking responsible for about 20% of CVD deaths in this population. The magnitude of the risk attributable to tobacco use provides a compelling reason why clinicians who care for patients with CVD need to put as high a priority on addressing tobacco use as they do on managing other cardiovascular risk factors such as hypertension or hyperlipidemia.

Worldwide, >1 billion individuals use tobacco products, but the prevalence varies considerably by gender and geography.(1) The 2015 Global Burden of Disease Study, representing 195 countries and territories, estimated that 25% of men and 5.4% of women worldwide smoked daily.(1) Although tobacco use was previously more common in high-income countries, the burden has now shifted to low and middle-income countries, where an estimated 80% of today's smokers live.(5) In the U.S., adult cigarette consumption has been declining since the 1960s when the health consequences of tobacco use first became widely known, launching a variety of tobacco control policies by federal, state, and local governments (Figure 1).(4) Combustible cigarettes are the most common tobacco product used by U.S. adults.(6) In 2016, 15.5% of adults reported currently smoking cigarettes; of these, 76% smoked daily and 24% smoked less often than daily.(7) Smoking prevalence is disproportionately higher among adults who have less education, lower incomes, and comorbid psychiatric and other substance use disorders.(7,8) Cigarette smoking rates among adolescents are currently at their lowest level in decades, with 8.0% of high school students and 2.2% of middle school students in 2016 reporting cigarette smoking in the past 30 days, the definition for current smoking among adolescents.(9)

Increasingly, cigarette smokers are using more than one type of tobacco product. In the 2013–2014 Population Assessment of Tobacco and Health survey, 40% of U.S. adolescent and adult tobacco users reported using multiple products (10). These include cigars, cigarillos, pipes, waterpipes (also called hookah or shisha), and smokeless tobacco. However, the most common non-cigarette tobacco product used by both youths and adults in the U.S. is the electronic cigarette (e-cigarette) (10). This product is a battery-powered device that heats a liquid, usually containing nicotine, to create an aerosol that the user inhales. It is the first of a new category of alternative tobacco products that aim to reduce the health risks of cigarettes by not burning tobacco to produce smoke. In 2015, approximately 3.5% of U.S. adults reported past-30-day e-cigarette use (6), while 11.3% of high school students and 4.3% of middle school students reported using e-cigarettes in the past 30 days (9).

An even newer alternative tobacco product is the heat-not-burn device which creates an aerosol by heating tobacco without burning it (11). It differs from e-cigarettes in heating tobacco, while e-cigarettes heat a solution containing nicotine, a humectant like propylene

glycol or vegetable glycerin, and flavoring. Heat-not-burn products are already marketed in 30 countries, but are not yet sold in the U.S.(11).

Pathophysiological Effects of Tobacco Smoking on the Cardiovascular System

Epidemiologic risks of tobacco use for cardiovascular disease—Cigarette smoking is a major risk factor for many cardiovascular diseases. Current smokers have significantly higher odds of myocardial infarction (MI) (OR 2.87, 95% CI 2.58–3.19),(12) and a two- to three-fold higher risk of death from ischemic heart disease than never smokers. (13) Smokers with known coronary artery disease are also at higher risk of sudden cardiac death compared to never smokers (hazard ratio 2.47, 95% CI 1.46–4.19).(14) Smoking approximately doubles the risk of death from stroke for current smokers compared to never smokers.(13)

The association between smoking and CVD is non-linear such that even a few cigarettes a day disproportionately increases cardiovascular risk.(15) Smoking just one cigarette daily is also associated with a higher stroke risk.(15) These data indicate that there is no safe level of cigarette consumption, and that the goal of treatment should be complete cigarette abstinence.

Smoking acutely raises blood pressure, but epidemiological studies have generally not shown an association between smoking and hypertension.(16,17) Smoking has been associated with an increased risk of complications from hypertension, such as increased risk of death from hypertensive heart disease(18) and decline in renal function.(19)

Current smokers have two- to three-fold higher odds of peripheral artery disease (PAD) compared with nonsmokers,(20) and greater progression of arterial stiffness over 5–6 years. (21) In one study, smokers were more likely than nonsmokers with PAD to be hospitalized over one year and were more likely to be hospitalized for acute MI and coronary heart disease (CHD).(22) Smokers also have an increased risk of abdominal aortic aneurysm (AAA).(23) More years of smoking and being a current versus former smoker have been associated with higher odds of AAA.(23) Current smoking was associated with a faster aneurysm growth rate compared to former or never smoking in a 2012 meta-analysis.(24)

The incidence of atrial fibrillation is approximately 1.5 and 2 times higher in former and current smokers, respectively, compared to never smokers.(25) Ventricular arrhythmia risk is also higher among smokers.(26) Smokers have higher risk of heart failure and poorer outcomes compared to never smokers. Among adults aged 70–79 participating in the Healthy Aging and Body Composition Study, the risk of heart failure was higher for current smokers compared to never smokers.(27) The Studies of Left Ventricular Dysfunction study, which included patients with a left ventricular ejection fraction below 35%, found a higher relative risk of all-cause mortality and congestive heart failure(CHF)-related mortality among current smokers than current non-smokers.(28) That study also found higher risk of hospitalization for CHF and higher risk of MI among current smokers compared to non-smokers.

Individuals who continue to smoke after a cardiovascular event or revascularization have poorer outcomes, highlighting the urgency of providing tobacco use treatment in these settings. After MI, continuing smokers have higher risk of recurrent coronary events than smokers who quit (RR 1.51, 95% CI 1.10–2.07).(29) Continued smoking after a stroke or transient ischemic attack, compared to quitting smoking, increases the 5-year risk of another stroke, MI, or death.(30) Continued smoking after an intervention for coronary artery disease also leads to negative outcomes. Among 985 coronary artery bypass graft surgery (CABG) patients followed for a median of 20 years, continuing smokers had a greater risk of all-cause mortality (RR 1.68, 95% CI 1.33–2.13) and cardiac death (1.75, 1.30–2.37) than smokers who quit.(31) Continuing smokers were also more likely than those who quit to require another procedure (e.g. CABG or angioplasty). Among 5450 smokers followed for up to 16 years after successful percutaneous revascularization, persistent smoking was associated with increased risk of all-cause mortality (RR 1.76, 95% CI 1.37–2.26) and Q-wave MI (2.08, 1.16–3.72) compared to never smoking (32).

Secondhand tobacco smoke exposure—Secondhand tobacco smoke exposure (TSE) by nonsmokers is associated with an increased risk of both CHD and stroke. In a meta-analysis, the relative risk for CHD among nonsmokers with TSE compared to nonsmokers without TSE was 1.31 (95% CI 1.21–1.41).(33) In another meta-analysis, TSE by nonsmokers was associated with increased risk of stroke (RR 1.25, 95% CI 1.12–1.38) (34).

Smokeless tobacco—While smokeless tobacco has the advantage of avoiding exposure to the products of combustion, it exposes users to varying amounts of nicotine and carcinogenic tobacco-specific nitrosamines and metals.(35) Most epidemiologic data on the CVD risk of smokeless tobacco comes from Sweden where a substantial proportion of men use snus, a smokeless tobacco product lower in nitrosamines and other contaminants than most other smokeless tobacco products. Most studies have not found an increased risk of non-fatal CVD among smokeless tobacco users.(36) However, a 2009 meta-analysis using data from Sweden and the U.S. found that smokeless tobacco use was associated with increased risk for both fatal MI (RR 1.13, 95% CI 1.06–1.21) and stroke (1.40, 1.28–1.54). (37) Following MI, continuing snus users have a substantially higher two-year mortality compared to those who quit.(38) In the 52-country INTERHEART case-control study, chewing tobacco use was associated with increased odds of acute MI compared to never tobacco use,(39) and individuals who used both cigarettes and chewing tobacco had higher odds of acute MI than users of either product alone.

Pathophysiologic mechanisms of increased risk—Cigarette smoke contains over 7,000 toxic chemicals, including several components implicated in CVD and 69 known carcinogens.(4) The constituents of tobacco smoke contribute to CVD via multiple mechanisms, including adverse effects on hemodynamics, endothelial dysfunction, thrombosis, inflammation, lipid abnormalities, and arrhythmogenesis (Figure 2, Table 1). While nicotine is the primary constituent of cigarette smoke that causes addiction and produces the hemodynamic effects associated with smoking, most of the excess cardiovascular risk of smoking is attributable to the effect of other cigarette smoke constituents. The free radicals and reactive oxygen species from cigarette smoke cause

endothelial dysfunction, platelet activation, and promote atherosclerosis through oxidization of low density-lipoprotein (LDL).(40) Particulate matter also causes oxidative stress, endothelial dysfunction, and platelet activation, and has effects on the autonomic nervous system.(41) These effects can be observed even after exposure to secondhand smoke.(33,42) Other chemicals in cigarette smoke that may contribute to CVD include carbon monoxide, carbonyls (such as acrolein), polycyclic aromatic hydrocarbons, and metals (43).

Taken together, the effects of cigarette smoke contribute to an environment that promotes plaque formation and thrombosis, produces an imbalance between myocardial blood supply and demand, and increases the likelihood of arrhythmogenesis, increasing the risk of cardiovascular events. Additionally, cigarette smoking appears to interact with genetic factors underlying CVD risk.(44) For example, the cardio-protective effects of a variation in a gene locus near the ADAMTS7 gene were diminished among those who smoked compared to never smokers.(45) Further studies on genetic and environmental factors may better characterize mechanisms of risk and identify individuals at higher risk for smoking-related CVD.

Factors Associated with Smoking Initiation and Cessation

Natural history of tobacco use—Tobacco use can be characterized as a chronic disease that begins in childhood because nearly all cigarette smokers report that they smoked their first cigarette during adolescence and then continue to use tobacco for decades.(46) Over 80% of U.S. adults who report ever trying a cigarette did so by age 18, and 98% did so by age 26.(47) Additionally, 96% of adults who ever smoked cigarettes daily report starting to smoke daily by age 26.(47) Initially, adolescents experiment with an occasional cigarette, and a subset of these individuals progress over varying periods of time to regular cigarette smoking. Once smoking becomes an established behavior, reducing the risk of tobacco-related disease requires smoking cessation. Promoting cessation is the primary task of clinicians who care for adults.

Quitting smoking is a dynamic process characterized by periods of regular smoking, reduced smoking, and no smoking.(48) Most smokers make numerous attempts to quit before they achieve success.(49) Among adult smokers responding to the 2015 National Health Interview Survey, 68% reported that they wanted to stop smoking and 55% had made a quit attempt in the past year, but only 7% had succeeded in quitting smoking.(50) However, most smokers continue to try to quit and eventually many of them succeed, because 59% of all living adults in the U.S. who have ever smoked have quit smoking as of 2016.(7) One reason for the low success rate is that despite the availability of effective evidence-based treatments for quitting smoking (51), most smokers (69%) do not use them in their attempts to quit (50).

Nicotine dependence—Tobacco use is tenacious because it is both a physical dependence on nicotine and a deeply-ingrained learned behavior. Nicotine binds to nicotinic acetylcholine receptors in the brain, leading to the release of neurotransmitters with rewarding and reinforcing effects.

Repeated use leads to the upregulation of nicotine receptors, tolerance, and physical dependence (4). The symptoms of nicotine dependence can develop rapidly, appearing after adolescents have only smoked a few cigarettes for a short period of time and well before adolescents have transitioned from initial experimentation to becoming regular daily cigarette smokers.(52) Nicotine dependence symptoms, in turn, are associated with future increases in cigarette consumption,(53) suggesting a bidirectional association between nicotine dependence and cigarette consumption. Stopping smoking is associated with nicotine withdrawal symptoms that include cravings, irritability, anxiety, restlessness, dysphoria, impaired concentration, and hunger.(54) Specific symptoms and the duration of withdrawal vary among smokers; while some smokers' symptoms resolve within 2 weeks, others experience cravings even after 6 months of smoking abstinence (55).

The learned behavior of smoking derives from its association with specific triggers that prompt craving to smoke and contribute to repeated use. Triggers can include smoking in personal or social circumstances, drinking coffee or alcohol, seeing other smokers, or even seeing objects such as cigarette packs or advertisements. Many smokers report smoking in response to stress or other negative emotional states, and quitting smoking is particularly difficult for such smokers. This behavior is likely due both to the positive effects of nicotine and to the fact that smoking reverses the dysphoria and cognitive impairment induced by nicotine withdrawal in addicted smokers.

Smoking initiation—Multiple factors influence both the initiation and maintenance of tobacco use. The socioecological model provides a framework for categorizing these factors into levels of influence organized into an ascending order of intra-individual, interpersonal, community/organizational, and societal/policy levels (Central Illustration) (56).

At the individual level, smoking among adolescents is more common in non-Hispanic whites than blacks or Hispanics and among adolescents with lower socioeconomic status as measured by their educational goals or parental educational attainment (47). Psychological factors associated with smoking initiation among adolescents and young adults include greater risk taking and impulsivity (46), stress (57), depressive symptoms (58), and anxiety (59). Genetic factors also influence both smoking initiation and development of nicotine dependence, and appear to play a larger role in the latter (60).

At the interpersonal level, the strongest effect on youth smoking is the influence of peers. Adolescents who smoke are often friends with other smokers, and those who do not smoke but have friends who smoke are more likely to start smoking.(61) Perceived prevalence of smoking among peers has also been associated with subsequent smoking among adolescents. A study of eighth graders found that nonsmokers who estimated that a higher percentage of eighth graders at their school were smokers were more likely to be smoking one year later.(62) Evidence for family influences on adolescent smoking is mixed: while some studies have found that parental smoking predicts smoking among adolescents, other studies have not (47).

Broader community and policy factors also influence smoking initiation. A robust body of evidence demonstrates that both the cost and marketing of tobacco products strongly

influence smoking initiation. Higher prices have been clearly associated with reduced cigarette smoking prevalence.(63) This includes effects on both adult cigarette consumption and cigarette use by youth(64) and young adults.(65) Federal, state, or local governments can increase the price of cigarettes by raising tobacco excise tax rates. This is one of the strongest policy tools available to discourage smoking initiation.

Tobacco marketing, which includes both advertisements and promotional efforts such as sponsorship of events attractive to teens, is also strongly associated with both smoking initiation and continued smoking among adolescents.(47) Adolescents exposed to tobacco promotions and depictions of tobacco in media have more favorable tobacco-related attitudes and are more likely to start smoking.(66) In one study of adolescents who were not susceptible to smoking, those who had tobacco promotional items or who reported that they would use them were more likely to initiate cigarette smoking.(67)

Smoke-free laws and policies are also associated with a lower smoking prevalence by youth and young adults. Living in an area with 100% smoke-free laws in workplaces has been associated with lower odds of smoking initiation among adolescents and young adults (OR 0.66, 95% CI 0.44–0.99).(68) Adolescents and young adults who live in areas with 100% smoke-free bars are also less likely to be current smokers (OR 0.80, 95% CI 0.71–0.90).(68) Smoke-free laws have also been associated with the adoption of voluntary smoke-free policies in cars and homes,(69) which are associated with lower adolescent smoking prevalence.(70) Reducing the supply of cigarettes, such as by enforcing laws that prohibit tobacco sales to minors, can reduce illegal sales.(71) However, the effect of such interventions on policies on smoking behavior may be diminished by the fact that youth report getting cigarettes from a variety of sources and not only by purchasing tobacco products.(72) Recently, raising the legal age of tobacco purchase from 18 to 21 years has been advocated as a strategy to reduce adolescent tobacco use. A National Academy of Science Report concluded that “increasing the minimum age of legal access to tobacco products will likely prevent or delay initiation of tobacco use by adolescents and young adults” and supported current advocacy efforts to increase the legal age of smoking from 18 to 21 years (46).

Smoking cessation—Stopping smoking requires an individual to overcome nicotine dependence and also abandon a deeply-ingrained rewarding behavior. Barriers to cessation can be conceptualized using the socioecological model (Central Illustration) (56). At the intra-individual level, nicotine dependence is a major reason for difficulty quitting smoking (73). Dependence is stronger in certain smokers, such as smokers with low socioeconomic status, mental illness, and other substance use disorders (74). These individuals often have lower success in their attempts to quit, with or without treatment.

At the interpersonal level, the smoking status of the spouse and other household members is influential. Living with other smokers has been associated with reduced smoking cessation, while having a ban on smoking in the home has been associated with increased cessation. (75) In one study, a smoker’s chance of smoking was reduced by 67% if a spouse quit smoking and 36% if a friend quit smoking.(76) Another study found that smokers who reduced their number of smoking friends were more likely to quit smoking than smokers

who had no change in smoking friends.(77) A smoker's perception of strong social support for quitting from family and friends is also associated with greater success in quitting.(78).

Community and policy-level interventions can also promote smoking cessation. Smokers whose worksites have smoke-free policies are more likely to both reduce cigarette use and quit smoking compared to smokers without smoke-free worksites.(79) Cigarette prices are inversely associated with smoking behavior,(80) and increases in tobacco excise taxes that lead to higher prices for cigarettes can reduce smoking prevalence among adults.(81) Comprehensive tobacco control programs that include mass media campaigns to educate smokers about quitting resources can be effective in promoting cessation among adults.(82)

The Role of Preventive Action

Health benefits of smoking cessation—Quitting smoking reduces the risk of overall mortality among adult smokers, with health benefits observed even among smokers who quit after the age of 65 or after the development of a tobacco-related disease.(13,73,83) The greatest mortality benefit occurs among smokers who quit smoking by the age of 40, who reduce their risk of dying from smoking-related disease by 90%,(3) but mortality benefits also extend to smokers over the age of 70.(83) In addition to mortality benefits, smokers who quit reduce their risk of developing tobacco-related diseases, such as cardiac disease, pulmonary disease, and malignancy.(73) Thus, smoking cessation should be prioritized for smokers of all ages.

The benefits of smoking cessation begin within hours of quitting smoking with reductions in heart rate and blood carbon monoxide levels.(84) The effects of smoking on platelet activation decrease within days.(85) The risk of tobacco-related diseases declines at different rates. For CHD, the excess risk among former smokers declines rapidly, falling to half of the risk of continued smoking after 1 year of cessation and reaching the level of nonsmokers within 15 years.(84) The excess risk of stroke is almost completely eliminated by 5 to 15 years after cessation.(84) In contrast, the reduction in excess lung cancer risk occurs more gradually(86) and remains elevated even for long-time former smokers compared to never smokers.(84)

Smoking cessation reduces CVD risk rapidly even among smokers with pre-existing disease, making treating tobacco use a priority for secondary CVD prevention. Among smokers with CHD, quitting smoking was associated with a 36% reduction in cardiovascular mortality over two years compared to continued smoking in one systematic review.(87) Smokers who quit after MI, compared to those continuing to smoke, reduce subsequent mortality by 15% to 61%, have a better health-related quality of life and less angina.(88,89) Smoking cessation also has positive health effects for smokers with other tobacco-related diseases. For smokers with COPD, cessation slows the rate of decline in lung function,(90) reduces symptoms and the odds of exacerbation,(91,92) and lowers all-cause mortality.(93) For smokers with lung cancer, smoking cessation can reduce the risk of recurrence, development of a second primary cancer, and mortality (94).

Unlike the health benefits of smoking cessation, reducing cigarette consumption without eventually quitting cigarettes appears to produce a relatively small health benefit.(95)

Smoking reduction has not been associated with decreased overall mortality or mortality from tobacco-related diseases (2,96). Smoking even one cigarette per day is associated with a higher risk of CHD and stroke (15). Therefore, smokers' goal for improving health should be stopping all cigarette smoking.

Health benefits of reducing secondhand tobacco smoke exposure—To protect nonsmokers from the health risks of secondhand tobacco smoke exposure, governments and private-sector organizations have adopted a variety of laws and policies prohibiting smoking in public places, workplaces, restaurants, bars, and other locations. Comprehensive smoke-free policies have measurable clinical benefits. In a 2012 meta-analysis, comprehensive smoke-free laws were associated with reductions in hospitalizations or deaths from acute myocardial infarction (RR 0.85, 95% CI 0.82–0.88), other heart disease (0.61, 0.44–0.85), cerebrovascular accidents (0.84, 0.75–0.94), and respiratory disease (0.76, 0.68–0.85), and more comprehensive policies were associated with larger risk reduction.(97) A 2014 meta-analysis also found that smoke-free laws were associated with reductions in preterm birth and hospital visits for asthma, but no significant difference in low birthweight.(98)

Evidence-based Tobacco Control Policies—A substantial evidence base supports the effectiveness of public policies to reduce tobacco use. Most tobacco control policies act by reducing the demand for tobacco products. Such measures include increasing the price of cigarettes by raising tobacco excise taxes, adopting smoke-free policies for indoor areas, mandating health warning labels on tobacco packages, and supporting mass media campaigns to educate the public and promote cessation. Other measures aim to reduce the supply of tobacco to adolescents by raising the legal age of tobacco purchase and actively enforcing these laws.

The World Health Organization assembled evidence-based tobacco control measures into a formal policy document, the Framework Convention on Tobacco Control (FCTC), which is essentially a public health treaty. It took effect in 2005 and the 181 countries that have ratified the FCTC have agreed to adopt its package of tobacco control measures.(99,100) The MPOWER acronym was introduced to help countries implement these policies (Table 2).(101) The implementation of the FCTC has been associated with increased adoption of advertising bans(102) and smoke-free legislation.(103) Countries that implemented the measures to reduce demand at the highest level have observed reductions in smoking prevalence.(104) However, some countries have yet to implement any of these measures, and the U.S. has not ratified the FCTC. Increasing adoption and effective implementation of effective tobacco control policies is a key worldwide public health priority.(101) Given the importance of tobacco abstinence for cardiovascular health, cardiologists can act as tobacco control advocates to help reduce smoking initiation among youth and young adults, and promote smoking cessation among adults at-risk for or already affected by CVD.

Harm reduction—Attaining complete abstinence, especially from combustible tobacco products, is the optimal way for a current smoker to reduce tobacco-related health risks, but not all tobacco users are willing or able to do so with current treatments. For these individuals, harm reduction is an alternate approach. This strategy recognizes that while nicotine is what maintains tobacco use, most of the health risks of tobacco use derive from

other constituents of tobacco smoke. Thus, nicotine-containing products exist on a risk continuum from less harmful to more harmful (Figure 3) (105). Harm reduction could be achieved by moving the population from higher to lower risk nicotine products. The U.S. Food and Drug Administration (FDA) adopted this strategy in 2017 when it announced a plan to regulate nicotine and tobacco products with the goal of reducing the use of combustible cigarettes and their associated morbidity and mortality (105).

One strategy that the FDA is exploring is mandating a reduction in cigarettes' nicotine content to a minimally-addictive level, estimated to be <0.4 mg per gram of tobacco.(106) Smoking very low nicotine content (VLNC) cigarettes, compared to usual cigarettes, has been shown to reduce smokers' nicotine exposure, dependence, and daily cigarette consumption.(107,108) A potential concern is that smokers will compensate for their reduced nicotine intake by smoking more cigarettes, thereby increasing their exposure to cigarette smoke's many other toxicants. So far, studies have found little evidence of compensation, but smokers do seek out other sources of nicotine.(109) Having lower-risk nicotine-containing products, such as nicotine replacement therapy (NRT) or e-cigarettes, readily available to smokers of VLNC cigarettes will likely be essential for the strategy to succeed.(110) A simulation model found that reducing cigarettes' nicotine content to minimally addictive levels would lead to a substantial reduction in tobacco-related mortality, despite uncertainty about the effects on smoking behaviors.(111)

A key component of the reduced nicotine strategy is to identify the appropriate regulatory approach to alternative sources of nicotine such as e-cigarettes.(112) Because they do not burn tobacco, e-cigarettes should pose less risk to users than cigarette smoke. A 2018 report from the U.S. National Academies of Sciences, Engineering, and Medicine concluded that e-cigarette aerosol exposes users to fewer toxicants than cigarette smoke and that e-cigarette use is likely to be less harmful than smoking cigarettes, although long-term health effects of e-cigarettes have yet to be determined.(113) The report found insufficient evidence at present of a risk from e-cigarettes on cardiovascular outcomes or measures of subclinical atherosclerosis.(113) Policies surrounding increased access to e-cigarettes for smokers trying to reduce their harm from cigarette smoking will need to be balanced against those limiting access to e-cigarettes by nonsmoking youth and young adults. Furthermore, these policies will need to continue to be reassessed as knowledge on the long-term health consequences of products such as e-cigarettes increases.

Guidance for Healthcare Providers

Screening and brief clinical interventions—According to national surveys, current smokers' interest in quitting smoking is high but their use of evidence-based treatments and the success of individual quit attempts remains modest.(50) At outpatient visits, 63% of patients are screened for tobacco use and only 25% of identified smokers are provided cessation treatment in the form of medication or counseling.(114) Clinicians who care for patients with CVD can narrow this gap by routinely screening for tobacco use and not only providing advice to quit, but also helping current smokers use evidence-based tobacco cessation treatment. Even brief advice from a physician can increase the likelihood of successful smoking cessation.(115) A 2015 Cochrane meta-analysis found that psychosocial

interventions for smokers with coronary heart disease increased smoking abstinence after 6–12 months (RR 1.22, 95% CI 1.13–1.32).(116) Additionally, clinicians can help nonsmokers avoid the health risks of secondhand tobacco smoke exposure on CVD by routine screening and advice to adopt smoke-free home and car policies.

A new diagnosis of CVD, acute MI, or acute coronary syndrome, or a cardiovascular procedure all serve as “teachable moments” that can motivate a smoker to attempt cessation. Among smokers hospitalized for cardiovascular disease, a Cochrane meta-analysis found that providing a smoking cessation intervention in the hospital and sustaining it post-discharge increased smoking cessation rates (RR 1.42, 95% CI 1.29–1.56).(117) However, only 7% of smokers with acute MI used smoking cessation medications in the early post-discharge period in a recent study (118).

Tobacco cessation treatment—Evidence-based smoking cessation treatments include medications and behavioral support. The combination of medication and counseling is the most effective approach because it allows management of both nicotine dependence and the conditioned behavior of smoking.(119) The U.S. Public Health Service’s 5As model provides a framework for brief office-based tobacco treatment. Its steps include *asking* about tobacco use, *advising* tobacco users to quit, *assessing* readiness to quit, *assisting* with quit attempts by providing medications or connecting individuals to counseling resources, and *arranging* follow-up to monitor success or roadblocks related to quitting.(120) An abridged 3-step model that recognizes that care is increasingly delivered by a health care team is helpful for busy clinicians; it includes *asking* about tobacco use, *assisting* those who use tobacco in trying to quit, and *referring* them to appropriate resources to help them accomplish their tobacco cessation goals (Figure 4) (121).

Tobacco cessation counseling can occur in-person or can be telephone-, mobile phone-, or web-based. In-person counseling can include individual(122) or group(123) settings. Telephone quit lines available in all U.S. states provide free services to smokers (1-800-QUIT-NOW). Proactive counseling in which counselors reach out to smokers over multiple sessions increases smoking cessation success.(124) Mobile phone-based interventions have also been effective in helping smokers quit.(125) In the U.S, the National Cancer Institute offers the SmokefreeTXT program (smokefree.gov/smokefreetxt). In contrast, acupuncture(126) and hypnotherapy(127) have not shown a consistent benefit for smoking cessation.

The medications approved by the U.S. FDA as smoking cessation aids are NRT (5 different products), varenicline, and bupropion (Table 3). Decisions on medications and combinations of medications should be customized based on patient preferences and side effect profiles. NRT helps to combat nicotine withdrawal symptoms by providing users with nicotine in either a long-acting (patch) or short-acting (gum, lozenge, inhaler, nasal spray) form. The nicotine patch provides nicotine transdermally throughout the day, while short-acting NRT acts more quickly but for a shorter duration. Use of NRT in any form increases smoking abstinence by 60% compared to placebo (RR 1.60, 95% CI 1.53–1.68).(128) To increase efficacy, the nicotine patch can be combined with short-acting NRT, which has been shown to be more effective than using one form of NRT (RR 1.34, 95% CI 1.18–1.51).(128)

Because of nicotine's sympathomimetic properties, the safety of NRT use in patients with CVD has been studied. NRT was associated with an increase in cardiovascular events, but not major cardiovascular events, when compared to placebo in a network meta-analysis that included individuals both with and without heart disease.(129) A study that specifically focused on outpatient smokers with CVD found no significant increase in cardiovascular events (death, myocardial infarction, cardiac arrest, or hospital admission for worsening angina, arrhythmia, or heart failure) among smokers receiving nicotine patch versus placebo. (130)

Varenicline is a partial nicotinic receptor agonist that more than doubles smoking abstinence rates compared to placebo (RR 2.24, 95% CI 2.06–2.43).(131) The EAGLES trial, which randomized more than 8000 smokers in 16 countries to varenicline, bupropion, nicotine patch, or placebo in a 1:1:1:1 ratio, found a significantly higher 6-month abstinence rate for the varenicline group compared to all other groups.(132) In a randomized trial of smokers with stable CVD, treatment with varenicline increased the odds of continuous abstinence at 1 year over placebo (OR 3.14, 95% 1.94–5.11).(133) A randomized trial of smokers with acute coronary syndrome found a higher rate of continuous abstinence at 24 weeks and a higher point- prevalence abstinence rate at 52 weeks in those taking varenicline vs. placebo. (134,135)

Because varenicline has nicotine-like effects, concerns have been raised about a potential cardiovascular risk of the drug. The bulk of available evidence does not suggest an elevated CVD risk when varenicline is used in smokers with or without CVD. The CATS trial, which examined cardiovascular events in over 8000 smokers from the EAGLES trial, found no evidence of increased cardiovascular events compared to bupropion, nicotine patch, or placebo.(136) The trial was not limited to smokers with CVD, but participants were middle-aged smokers, many of whom had other CVD risk factors. Although one meta-analysis of earlier randomized trials had reported an increased risk of CVD events among smokers using varenicline,(137) subsequent larger meta-analyses(129,138–140) and several large retrospective cohort studies(141–143) found no evidence of a significantly increased CVD risk with varenicline use. Recently, an observational study using Canadian prescription and health outcome databases reported an increase in cardiovascular events among smokers taking varenicline compared to a self-controlled time interval,(144) but limitations of the study design have been noted (145).

Cytisine, a plant alkaloid, is a partial nicotinic receptor agonist, like varenicline. Cytisine has demonstrated efficacy for smoking cessation in multiple clinical trials,(146) and has been used for this purpose in Eastern Europe for several decades. Efforts to develop cytisine as a smoking cessation aid in the U.S. are underway.

Bupropion increases levels of norepinephrine and dopamine and is approved both as an antidepressant and for smoking cessation. Bupropion increases smoking cessation rates compared to placebo or control.(132,147) Two studies of smokers hospitalized with acute coronary events did not find increases in smoking cessation in smokers who received bupropion versus placebo.(148,149) Bupropion treatment does not appear to be associated

with an increase in major adverse cardiovascular events.(129) Contraindications to use of bupropion include seizure disorder or having a high risk for seizure.

In 2009, concern about possible neuropsychiatric events with both varenicline and bupropion led the FDA to require both drugs' packages to carry a boxed warning. Subsequently, the EAGLES trial, which included individuals with and without mild-moderate psychiatric illness, showed no increase in adverse neuropsychiatric events among smokers receiving varenicline or bupropion compared to those receiving NRT or placebo (132). In 2016, FDA removed the boxed warning requirement for varenicline and bupropion.

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Abbreviations

CVD	cardiovascular disease
e-cigarette	electronic cigarette
MI	myocardial infarction
CHD	coronary heart disease
CHF	congestive heart failure
AAA	abdominal aortic aneurysm
CABG	coronary artery bypass grafting
TSE	tobacco smoke exposure
FDA	Food and Drug Administration
NRT	nicotine replacement therapy

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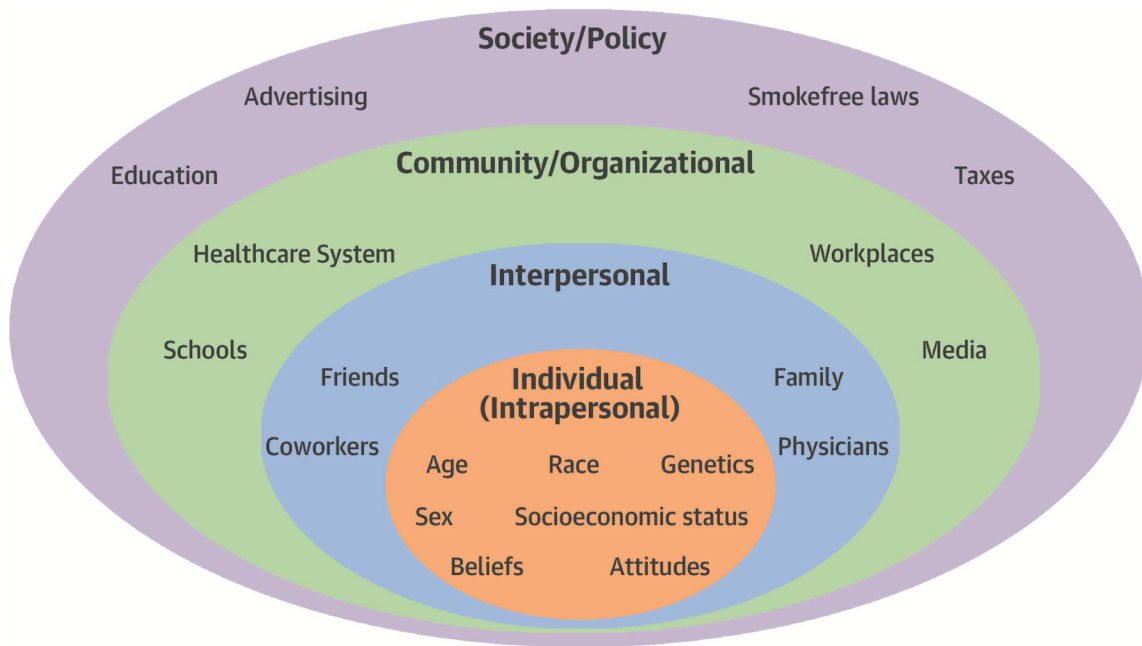
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Central Illustration. Socio-ecological model of factors associated with smoking initiation and continued smoking.

Various individual, interpersonal, community/organizations, and societal/policy factors play a role in why individuals start smoking and continue to smoke. Interventions targeting each of these factors can help to reduce smoking prevalence.

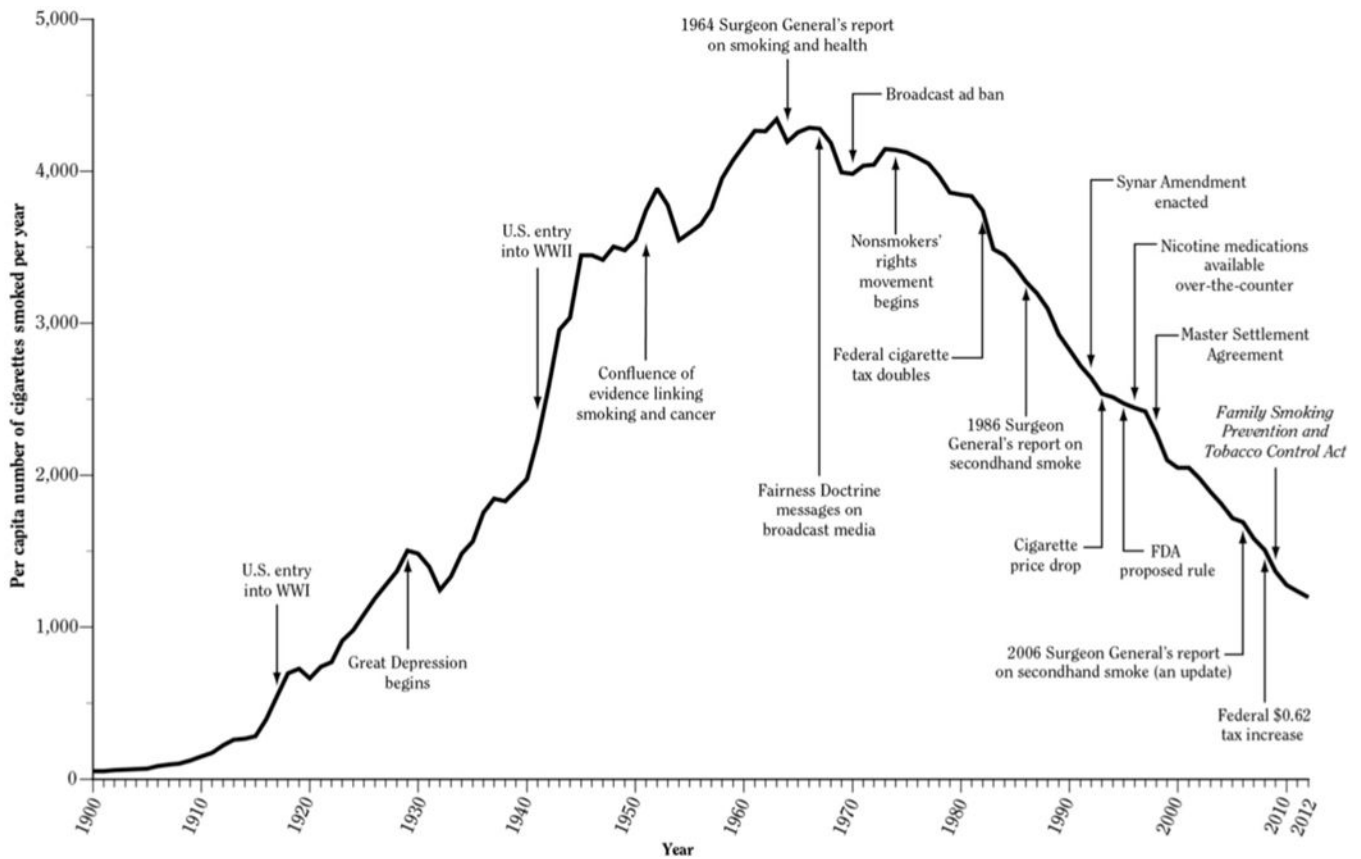


Figure 1. Per capita cigarette consumption per year among U.S. adults from 1900 to 2012. Cigarette consumption has been declining since the 1960s, during which time tobacco control policies have been adopted at local and national levels. From: US Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General. *Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.* 2014.

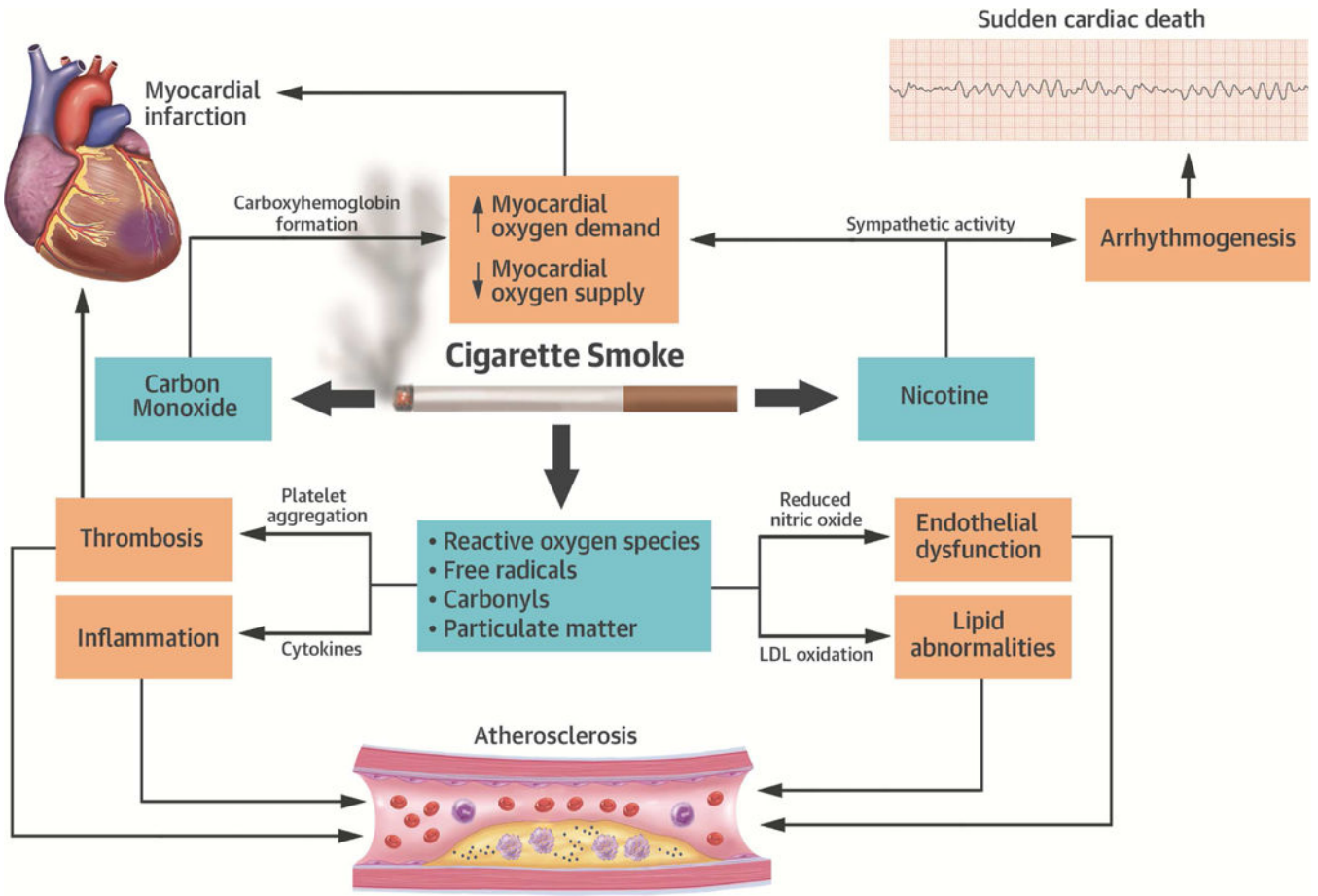


Figure 2. Mechanisms by which smoking causes cardiovascular disease.

The major components of cigarette smoke that contribute to cardiovascular disease include nicotine, carbon monoxide, reactive oxygen species, free radicals, carbonyls (such as acrolein), and particulate matter.

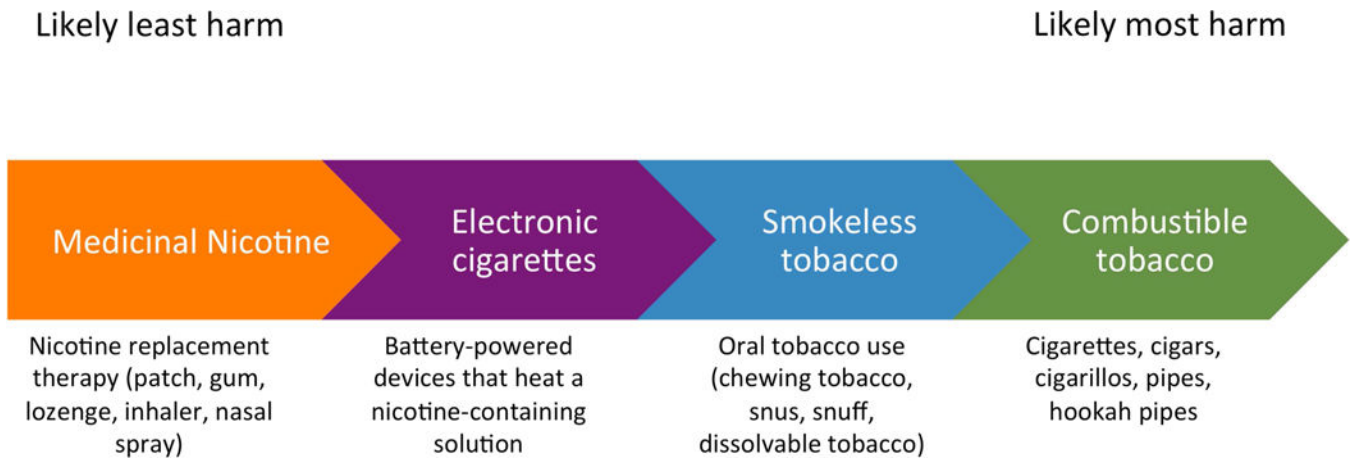


Figure 3. Risk continuum of nicotine-containing products.

Nicotine comes in many forms with varying degrees of potential harm to users. Medicinal nicotine, such as that contained in nicotine replacement therapy, is least likely to cause harm, while combustible tobacco, such as cigarettes, is most likely to cause harm. It is not known where heat-not-burn tobacco (also known as heated tobacco) products fall on this spectrum given the limited evidence on their health effects.

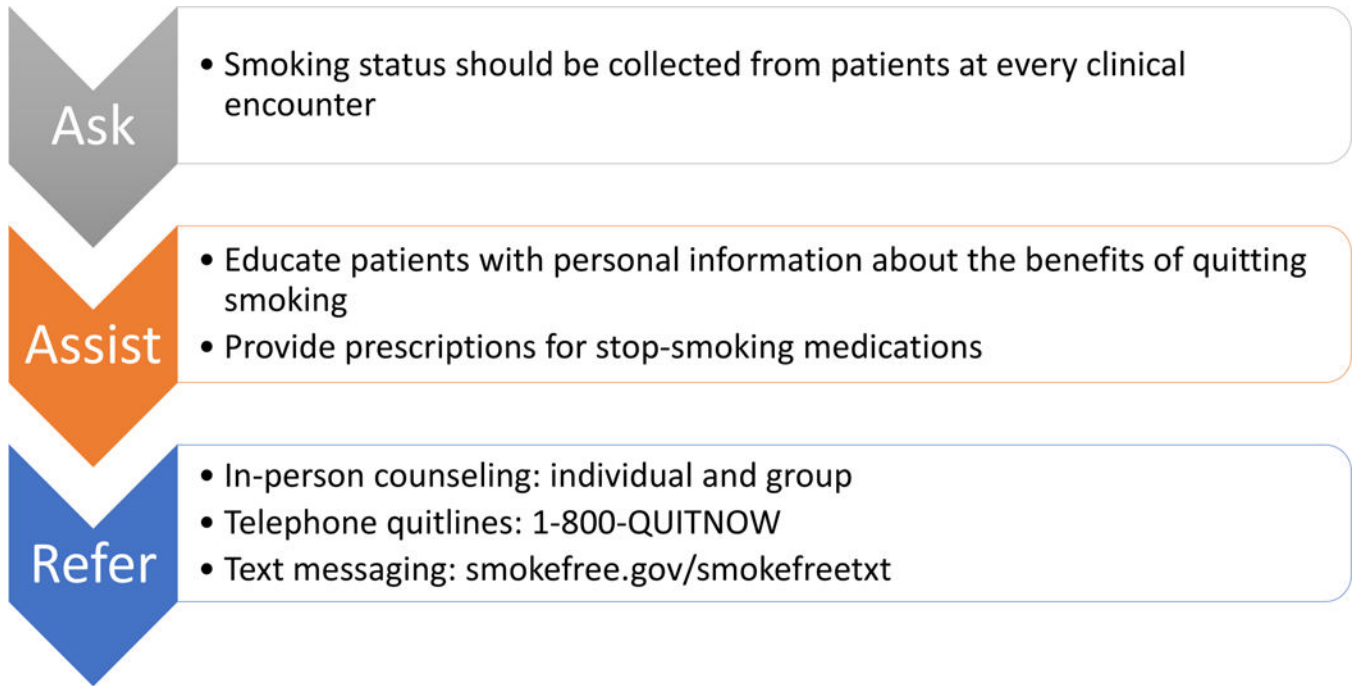


Figure 4. The Ask, Assist, Refer tobacco cessation intervention. Providers can use this tool to screen for tobacco use among all patients, and refer them to appropriate resources to help with smoking cessation.

Table 1.

Mechanisms of increased cardiovascular risk associated with cigarette smoking

Cardiovascular effect	Pathophysiological mechanism
<p><u>Hemodynamic changes</u></p> <ul style="list-style-type: none"> • ↑ heart rate • ↑ contractility • ↑ blood pressure • ↑ myocardial oxygen demand • ↓ myocardial oxygen supply • Altered coronary blood flow 	<ul style="list-style-type: none"> • Nicotine activates the sympathetic nervous system(44,73) • In general, nicotine ↑ coronary blood flow in response to increased myocardial work • Smoking leads to vasoconstriction in individuals with coronary artery disease(150) • Reduced oxygen delivery by red blood cells containing carboxyhemoglobin (from carbon monoxide in cigarette smoke)(44)
Endothelial dysfunction and damage	<ul style="list-style-type: none"> • Occurs as a consequence of oxidative injury and chronic inflammation • ↓ availability of nitric oxide, which normally acts as an endothelial cell vasodilator; reduces leukocyte adhesion, and prevents platelet aggregation(151)
Hypercoagulability and thrombosis	<ul style="list-style-type: none"> • ↑ platelet activation • ↓ availability of nitric oxide • ↑ blood viscosity due to polycythemia from chronic carbon monoxide exposure and relative hypoxia • ↑ plasminogen activator inhibitor type 1(152) • ↓ tissue plasminogen activator (tPA) release from the coronary vasculature(153) • ↑ expression of tissue factor in atherosclerotic plaques(154)
Chronic inflammation	<ul style="list-style-type: none"> • Enhanced leukocyte adhesion to vascular endothelium(155) • ↑ levels of inflammatory cytokines such as interleukin-6,(156) interleukin-1b, and tumor necrosis factor-alpha(157) • Smokers have higher levels of the inflammatory markers high-sensitivity C-reactive protein and fibrinogen(158)
Lipid abnormalities	<ul style="list-style-type: none"> • ↓ high density lipoprotein • ↓ low density lipoprotein and triglycerides(159) • ↑ levels of oxidized low-density lipoprotein(160)
Arrhythmogenesis	<ul style="list-style-type: none"> • Nicotine may promote myocardial remodeling and fibrosis,(161) likely related to beta-adrenergic stimulation • Nicotine-mediated catecholamine release may contribute to ventricular arrhythmia and sudden cardiac death
Other	<ul style="list-style-type: none"> • ↑ risk of developing type 2 diabetes(162) likely due to greater insulin resistance among smokers than nonsmokers,(163) and believed to be mediated by the sympathomimetic effects of nicotine and nicotine-mediated activation of AMP-activated protein kinase(164) • ↑ risk of coronary spasm(165)

Table 2.

WHO MPOWER Measures(101)

Measure		Examples of tobacco control actions
M	Monitor tobacco use and prevention policies	Conduct surveys to monitor tobacco use by adults and adolescents
P	Protect people from tobacco smoke	Enact smoke-free laws and policies in public places, workplaces, restaurants, bars
O	Offer help to quit tobacco use	Insure that health care providers assess tobacco use, advise tobacco cessation, and offer behavioral and pharmacological assistance to quit.
W	Warn about the dangers of tobacco	Conduct mass media campaigns to educate children and adults about health risks and addictiveness of tobacco, promote use of cessation resources. Require warning labels on tobacco packages.
E	Enforce bans on tobacco advertising, promotion, and sponsorship	Restrict tobacco industry sponsorship of events, distribution of free samples.
R	Raise taxes on tobacco	Increase tobacco excise tax rate to raise the price of tobacco products.
WHO, World Health Organization		

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Table 3.

Medications Approved by the U.S. Food and Drug Administration for Smoking Cessation

Medication	Dosing	Common Side Effects	Available over the counter?
Nicotine patch	>10 cigarettes/day: 21mg to start, taper after 6 weeks 10 cigarettes/day: 14mg to start, taper after 6 weeks	Redness/irritation at patch site, sleep disturbance	Yes
Nicotine gum	Smokes first cigarette 30 minutes of waking: 4mg every 1-2 hours Smokes first cigarette >30 minutes of waking: 2mg every 1-2 hours	Oral issues, nausea, heartburn, hiccups	Yes
Nicotine lozenge	Smokes first cigarette 30 minutes of waking: 4mg every 1-2 hours Smokes first cigarette >30 minutes of waking: 2mg every 1-2 hours	Oral issues, nausea, heartburn, hiccups	Yes
Nicotine inhaler	10mg cartridges 6-16 times per day	Oropharyngeal irritation, cough	No
Nicotine nasal spray	1-2 sprays per nostril per hour	Nasopharyngeal irritation, sneezing, coughing	No
Varenicline	0.5mg daily for 3 days, then 0.5mg twice daily for 4 days, then 1mg twice daily	Nausea, abnormal dreams	No
Bupropion	150mg daily for 3 days, then 150mg twice daily	Insomnia, dry mouth	No