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Tobacco Use Disorder and Cardiovascular Health

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ABSTRACT

This narrative review examines the impact of cigarette smoking and the use of other tobacco and nicotine products on cardiovascular disease. Smoking increases the incidence of both acute and chronic cardiovascular diseases, and the harmful effects are substantially and relatively quickly reversible after quitting. Recommended cessation treatment includes offering pharmacotherapy, counseling which should emphasize the rapid risk reduction that occurs after quitting, and adequate follow-up contacts. Although most research on cardiovascular disease in relation to tobacco use has focused on cigarette smoking, we also review available data related to other combustible tobacco products, smokeless tobacco, electronic nicotine delivery systems, and secondhand smoke. We

discuss the implications of smoking on clinical management of patients with heart disease and newer developments with potential relevance to treatment of such patients.

Keywords: nicotine, tobacco, cardiovascular disease

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and premature death, responsible for 17.9 million deaths annually, corresponding to 31% of all deaths globally.(1) Most CVD deaths are due to coronary heart disease (CHD) and stroke. Tobacco use is among the leading causes of CVD, accounting for up to 30% of CVD deaths, depending on the country.(2) The most widespread and lethal form of tobacco use is cigarette smoking, which is associated in a life-long smoker with an average of at least 10 years of life lost.(3) CVD deaths occur both from active smoking and from secondhand smoke (SHS) exposure in non-smokers. Other forms of combusted tobacco use, such as cigars, pipes and waterpipe, have been associated with CVD as well, but their overall impact is far less than that of cigarette smoking because the prevalence of use is relatively low and the extent of smoke inhalation may be less. Smokeless tobacco use has been associated with CVD in some but not all countries, presumably related to differences in the nature of the products used. (4) There are as yet few data on CVD events in users of electronic cigarettes or heat-not-burn tobacco products.

2. EPIDEMIOLOGY

Cigarette smoking increases morbidity and mortality as a function of the number of cigarettes smoked per day, the duration of smoking, and the age at which a person quits smoking. The relationship between cigarettes per day and CHD risk is strikingly non-linear, with smokers of 5 or fewer cigarettes per day having 50% (or higher) the risk experienced by smokers of 20 cigarettes per day. (4-6) (Figure 1) Non-daily smoking in relation to number of cigarettes smoked per month also substantially increases CVD mortality.(5) Likewise, reduction in number of cigarettes smoked per day by 50% does not reduce CVD incidence.(7) The relative risk of CHD in smokers compared to non-smokers is much higher in younger than older people, because younger people have fewer other CHD risk factors.(8) (Figure 2) More than 50% of people who experience myocardial infarction below the age of 50 are smokers.(8) However, the absolute risk of smoking is much higher in older smokers because they have much higher CVD event rates in general. As discussed later in this paper, quitting smoking substantially reduces the risk of CVD events, with much of the benefit seen within the first one to two years.(9, 10) After 15 years of not smoking, CVD risks are markedly reduced and close to that of never smokers.(11) SHS is associated with an increased risk of CVD in non-smokers, with a 25-30% increased risk of CHD morbidity and mortality.(12) Hospital admissions for acute coronary syndrome decline in regions where legislative smoking bans are instituted.(13) Recent evidence supports a causal link between SHS smoke and stroke as well.(14)

3. CLINICAL CONDITIONS ASSOCIATED WITH CIGARETTE SMOKING

The vast majority of research on CVD in relation to tobacco use has focused on cigarette smoking, which is reviewed in this section. Later sections will review the data on CVD related to other tobacco products. Smoking increases the incidence of both acute and chronic CVD (Table 1).

a. Acute Effects

Acute events include myocardial infarction, stroke and sudden cardiac death, the latter of which is associated with the highest increased risk in smokers compared to non-smokers. Acute myocardial infarction in smokers is associated with a greater thrombus load and less severe underlying coronary atherosclerosis compared to non-smokers.(15) (Figure 3) Occlusion of the right coronary artery is more common in smokers than in smokers. Thus, if a smoker quits smoking after a heart attack the prognosis for future CVD events is better than that of a non-smoker, sometimes called the smoker's paradox.(16) After coronary revascularization (such as bypass surgery or coronary artery stenting),

smoking increases the risk of restenosis and recurrent myocardial infarction.(17, 18) Smoking reduces the protective effects of most antiplatelet drugs administered to patients with CHD.(19)

b. Chronic Effects

Smoking accelerates atherosclerosis in the coronary, cerebral, carotid and, to the greatest extent, in the aorta and peripheral arteries. Smoking reduces the exercise level at which angina pectoris and intermittent claudication occur, and causes vasospastic angina.(20) Cigarette smoking is associated with ventricular hypertrophy and incident heart failure.(21) Hypertensive heart and kidney disease are aggravated by smoking independent of CHD.(22) Smoking causes cardiac arrhythmias, including atrial fibrillation and ventricular arrythmias, the latter associated with sudden death.(23, 24)

4. PATHOPHYSIOLOGY OF TOBACCO-INDUCED CARDIOVASCULAR DISEASE

A number of reviews of the pathogenesis of smoking related CVD have been published in recent years.(25-28) In brief, the major mechanisms of accelerated atherosclerosis and acute CVD events include 1) inflammation, 2) thrombogenesis, 3) endothelial dysfunction, 4) hemodynamic stress, 5) arrythmogenesis, 6) insulin resistance and 7) lipid abnormalities (Figure 4). Most of the CVD risk is related to inhalation of tobacco combustion products. Oxidizing chemicals, volatile organic chemicals (such as acrolein) and particulates contribute to chronic inflammation and endothelial dysfunction, which promote atherogenesis, and contribute to a hypercoagulable state, which plays a major role in thrombosis seen in myocardial infarction and stroke. Carbon monoxide reduces oxygen delivery to the heart which aggravates ischemia, and increases red blood cell mass and blood viscosity, which also promotes thrombosis.

Nicotine may contribute to CVD primarily by activating the sympathetic nervous system.(29) This produces hemodynamic stress (increasing heart rate, blood pressure and myocardial work, as well as constriction of coronary arteries), produces insulin resistance and an increased risk of type 2 diabetes, and causes arrythmias which may contribute to fatal myocardial infarction and stroke. Nicotine also reduces HDL cholesterol and produces a more atherogenic lipid profile, while oxidation of LDL in coronary plaques by the smoke further promotes atherogenesis. As discussed later, the strongest evidence against nicotine per se as a major factor in CVD are data on lifelong Swedish snus users, who are exposed to high levels of nicotine with relatively low impact on CVD risk (see discussion of smokeless tobacco below).

With respect to SHS, many of the adverse effects of tobacco smoke, such as endothelial dysfunction and hypercoagulability are seen with very low levels of smoke exposure, supporting biological plausibility of causation.(30)

5. CARDIOVASCULAR DISEASE RISK FROM TOBACCO PRODUCTS OTHER THAN CIGARETTES

a. Cigars, pipes and water pipe

Cigar and pipe smoking potentially exposes a person to the same combustion products as cigarette smoking. The main differences in disease risk relate to extent of inhalation. Smokers of small cigars and cigarillos often inhale in the same way as cigarette smokers, whereas many smokers of large/premium cigars and pipes do not.(31) The extent of inhalation is determined in part by whether the person had been a cigarette smoker in the past. Former smokers or dual cigarette and cigar smokers are more likely to inhale more cigar smoke. The extent of inhalation has been determined by measuring increase in carbon monoxide levels. The smoke pH of cigars and pipes is generally higher than that of cigarette smoke, facilitating buccal absorption of nicotine, such that nicotine exposure can be substantial. Thus, the risk of CVD from cigar smoking depends on the type of cigar and the extent of inhalation, as well as frequency of use. Small cigars and cigarillos are inhaled like cigarettes,

often consumed daily and presumably carry the same CVD risk. Large and premium cigars tend not to be inhaled by primary cigar smokers, but may be inhaled by those who were cigarette smokers in the past. Also, many premium cigar users smoke cigars infrequently, thereby reducing or eliminating CVD risk. Unfortunately, most of the epidemiology on cigars and CVD does not specify the type of cigar smoked. Epidemiology studies for cigars in general suggest an increase in CHD deaths, less than seen in cigarette smokers, with variable results across studies.(31)

Traditional tobacco pipe smokers typically do not inhale smoke, as demonstrated by no elevation in carbon monoxide levels. Nicotine intake is similar to that of cigarettes, but there appears to be small or no increased CVD risk in exclusive pipe smokers.(32) Much of the epidemiology on pipe smoking and CVD combines cigar and pipe use, making reliable risk estimates difficult to ascertain.

Water pipe smoking consists of inhaling smoke from a fruit and tobacco mixture that is heated by charcoal and cooled by passage through water. The chemical constituents of water pipe smoke differ somewhat from burning tobacco with higher levels of carbon monoxide and a different profile of polycyclic hydrocarbons. Water pipe smoke can induce the same acute pathogenetic effects seen in cigarette smoking, except that the endothelial dysfunction caused by the smoke can be masked, at least acutely, by the vasodilatory effects of high levels of carbon monoxide.(33) Water pipe use is common among youth and young adults in Western countries, but use is generally occasional, such that the risk of CVD is probably low. However regular daily use is common in many Middle Eastern and Southeast Asian countries, and epidemiological studies among regular users find increases in CVD risk similar to that of cigarette smoking.(34, 35)

b. Smokeless Tobacco

Smokeless tobacco delivers on average similar amounts of nicotine daily to cigarette smoking, but without products of combustion.(36) Smokeless tobacco is sold in many forms around the world, with potentially different CVD toxicity.(4, 37) The best CVD epidemiology comes from Sweden, where snus, a fermented ground tobacco product that is sold in small pouches that can be inserted between the gum and lips, is widely used. Swedish snus is regulated by the government so that its carcinogen and other contaminant content is lower than many other smokeless tobacco products. Case-control studies have reported no increased overall risk of myocardial infarction or stroke, but do report a small increase in case fatality rate compared to non-tobacco using controls.(38, 39) Carotid intima-media thickness, a marker of subclinical atherosclerosis, in middle-aged men was higher in cigarette smokers but not snus users compared to never users, suggesting that snus use does not promote atherosclerosis.(40) One study of survivors of myocardial infarction found that among snus users, those who continued to use snus after the event had significantly higher mortality compared to those who quit.(41) Snus use has been associated in some studies but not all with an increased risk of diabetes, and in one study with an increased risk of heart failure, but not with atrial fibrillation.(42-44) These adverse effects of snus use could be related to the sympathomimetic actions of nicotine, including precipitation of fatal arrhythmias in people who have an ischemic cardiovascular event, or perhaps confounding factors. A recent meta-analysis found a small increased risk of heart disease and stroke in U.S. smokeless tobacco users, but not in Swedish snus users.(45) However, a pooled analysis of data from eight Swedish cohort studies found that exclusive snus use was associated with a small but significant increase in cardiovascular mortality (adjusted HR 1.27; 95% CI 1.15-1.41) compared to never users of tobacco.(46) Most recently a large Swedish cohort study found that after adjusting for smoking, snus use was not associated with myocardial infarction, heart failure atrial fibrillation, aortic aneurysm, stroke or CVD mortality; however, snus use was associated with an increased risk of stroke in never smokers.(47) While the risk appears to be considerably lower than that of cigarette smoking,

smokeless tobacco use likely poses some cardiovascular risk and should be discouraged in patients with CVD.

c. Electronic Nicotine Delivery Systems

Electronic nicotine delivery systems (ENDS), including electronic cigarettes (e-cigarettes) and tobacco heating products are battery-powered devices that heat a liquid or a tobacco rod to produce a nicotine-containing aerosol without combustion. In addition to nicotine, e-cigarettes typically contain the humectants propylene glycol (PG) and vegetable glycerine (VG) and various flavoring chemicals. While most of the harmful effects of tobacco smoking are related to the products of combustion, e-cigarettes produce an aerosol that contains oxidizing chemicals and thermal degradation products of PG/VG, which may include toxic chemicals such as acrolein, formaldehyde, acetaldehyde and various other cytotoxic chemicals.(48)

ENDS devices vary widely in their design, liquid components and heating temperatures. The higher the heating temperature, the greater the generation of oxidants and other thermal degradation products. However, the concentrations of these toxicants are generally much lower than are found in cigarette smoke. E-cigarettes do not generate carbon monoxide. They may deliver various metals in low concentrations, which derive from the coil and/or other devices components. E-cigarettes also generate particles in as great a number as do cigarettes, but these particles are liquid and dissipate quickly, whereas tobacco particles have carbonaceous cores. Whether particles from ENDS are as toxic as combustion particles is as yet unknown.

With respect to risks of secondhand exposure, unlike a cigarette, e-cigarettes generate little or no sidestream smoke. Secondhand aerosol is that which is exhaled by the users, which may consist of large plumes or wisps of vapor, depending on the device and the user. Furthermore, the liquid particles from e-cigarettes evaporate quickly (half-life 10-20 seconds), while secondhand cigarette smoke persists in the air for a much longer time (1.4 hours).(49)

ENDS can deliver nicotine at levels similar to those of cigarettes, which can produce the same sympathomimetic effects, including increased heart rate, blood pressure and myocardial contractility. Increased cardiac work increases the demand for oxygen and nutrients, which in people with CHD can induce cardiac ischemia.(50) Nicotine also releases catecholamines, that can trigger arrhythmias, which in the context of ischemic event could be lethal.

Preclinical studies with e-cigarette aerosols, flavor chemicals and nicotine show a variety of toxic effects including cytotoxicity, altered vascular function, inflammation and platelet activation that could contribute to CVD.(51) However, it is difficult to extrapolate preclinical studies to human disease risk owing to differences in doses and exposure schedules and the model test system. Acutely, e-cigarette use produces endothelial dysfunction assessed by flow-mediated dilation, but significant improvement in endothelial function is seen within one month when smokers switch from cigarettes to e-cigarettes.(52)

Because CVD from tobacco use generally takes many years to manifest, ENDS have been in use for relatively few years, and most adult e-cigarette users are former smokers, there are as yet no definitive epidemiology studies of ENDS and CVD. Published epidemiology studies are primarily cross-sectional and have serious methodological limitations. Thus, the risk of ENDS use for cardiovascular health is uncertain, but based on toxicant profile is thought to be much less than that of cigarette smoking. A few studies have described benefits of switching from cigarettes to e-cigarettes, including reduction of blood pressure, seen in both healthy smokers and those with hypertension.(53)

6. ASSESSMENT AND IMPLICATIONS OF SMOKING IN CARDIOVASCULAR DISEASE TREATMENT

Since smoking can cause or aggravate virtually any type of CVD and many of the harmful cardiovascular effects of smoking are substantially and relatively quickly reversible, screening for cigarette smoking and other tobacco use should be part of every healthcare encounter. The diagnosis of CVD should always trigger a strong message that quitting smoking as soon as possible is essential to maintaining cardiovascular health. Cigarette smoking should be considered in risk-stratifying adults 40 to 75 years old for primary CVD prevention interventions, such as prescription of statins.(54) The Framingham study-based atherosclerotic CVD risk estimator computes a patient's 10 year atherosclerotic CVD (ASCVD) risk based on data including age, sex, blood pressure, blood cholesterol level, history of diabetes and cigarette smoking history.(55) The 2019 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that initiation of statin treatment should be considered in smokers with a 10 year risk of 7.5% or higher, depending on whether enhancing factors are present.(54) Similarly, the smoking status affects (next to age, sex, blood pressure and cholesterol) the estimated 10 year risk of fatal CVD calculated with the Systematic Coronary Risk Evaluation (SCORE) risk charts of the European Society of Cardiology.(56) Where the estimated ASCVD risk is intermediate and the patient is a smoker, a coronary artery calcium score can further inform risk estimation.(54) Importantly, smoking is, in contrast to e.g. sex or family history, a reversible CVD risk factor and quitting smoking alone can change the patient's CVD risk category and thus also the indicated treatment.

Peripheral artery disease is highly prevalent in long-term cigarette smokers. The presence of peripheral vascular disease is a strong predictor of CHD, and should lower the threshold for CHD evaluation. Ultrasound screening for abdominal aortic aneurysm and evaluation of a potential intervention is recommended for men aged 65 to 75 years who have ever smoked.(57)

Drug Interactions and smoking

Smoking can impact the effects of medications in patients with CVD.(19, 58) Smoking accelerates the metabolism of cardiac drugs such as flecainide, which might require dose adjustment. Smoking reduces the anti-anginal effects of calcium channel blockers and beta blockers, and may require more intensive treatment.(59) Smoking is associated with coronary spasm that is less responsive to calcium blockers, thus requiring treatment with multiple coronary vasodilators. In the Beta Blocker Heart Attack Trial (BHAT), the survival and reinfarction benefit was greater in smokers vs non-smokers, possibly due to the antagonism of the sympathomimetic effects of nicotine.(60) Thus, beta blockers may be particularly important in smokers with CHD. Smoking has strong prothrombotic effects, which may reduce the efficacy of anti-thrombotic drugs, requiring more sustained use of anticoagulant drugs in patients after coronary revascularization or with severe CHD in general. On the other hand smoking enhances the conversion of clopidogrel to its active metabolite, enhancing the anti-platelet effect of this drug.(19, 61) Because of the prothrombotic effects of smoking, the risk of myocardial infarction and stroke is higher in women taking estrogen-containing oral contraceptives. It is recommended not to prescribe such contraceptives or hormone replacement therapy to women who are daily smokers and are 35 years or older. Smoking and other nicotine delivery systems may induce insulin resistance, such that hypoglycemic medication doses may need to be adjusted when a patient stops using tobacco.

7. TREATMENT

a. General Approach to Smoking Cessation

Smoking cessation in patients with CVD has been reviewed broadly in a recent consensus document from the American College of Cardiology.(62) Smoking can be conceptualized as a chronic relapsing

substance use disorder. Evidence-based smoking cessation strategies include counseling, which can range from a brief advice and self-help material to an intensive individual or group setting with motivational interviewing and cognitive behavioral training, and pharmacotherapy with first-line smoking cessation aids including nicotine replacement (combined patch plus short acting gum, lozenge or spray preferred), varenicline or bupropion.(62, 63) Counseling should emphasize that smoking cessation rapidly reduces the risk of future cardiovascular events. The usual treatment duration with all products is 3 months, but prolonged therapy may be necessary in patients at high risk of relapse at the end of pharmacotherapy. (62-64) Other types of interventions that might have the potential to assist smoking cessation (including ENDS) are discussed later in the section "Newer developments in treatment".

b. Cardiovascular safety of smoking cessation medications

In a recent meta-analysis of clinical trials involving patients with CVD, varenicline and bupropion have been shown to be effective in promoting smoking cessation, while evidence about nicotine replacement was inconclusive.(65) Regarding safety, the EAGLES trial was a large international smoking cessation trial involving more than 8000 smokers worldwide, stratified into psychiatric and non-psychiatric cohorts, comparing treatment with nicotine patch, varenicline, bupropion and placebo.(66) An extension of the EAGLES study examined cardiovascular events.(67) No differences were found in either neuropsychiatric or cardiovascular adverse effects by treatment. Cessation trials in smokers hospitalized with acute coronary syndrome have not raised any major concerns regarding cardiovascular safety, and continuing smoking is expected to be more harmful than any potential adverse effects related to the pharmacotherapy, but efficacy has been shown only with varenicline.(68)

c. Delivering Smoking Cessation Therapy in Clinical Settings

In outpatient offices and clinics, it is recommended that systems be put in place for routine screening of all patients for tobacco use, including e-cigarettes and information on SHS exposure. The clinician should provide definitive advice to quit, offer pharmacotherapy (appropriate to the patient's medical history and preferences) and connect or refer to behavioral therapy if the patient is interested. Larger clinics or practices should consider training staff to be smoking cessation counselors who can provide behavioral treatment in association with clinic visits. In all CVD patients, and especially in those with known CHD, advice should be provided on avoidance of SHS exposure. Follow-up of smokers in the process of quitting is important and can consist both of telephone calls from staff and return clinic visits. Given the nature of relapse with an addictive disorder, patients who relapse can be reassured and encouraged to try again in the near future.

A special subgroup of smokers consists of patients with mental illness. The population of people with mental illness is characterized by very high smoking rates (twice that of people without mental disease).(69, 70) Accordingly, people with mental illness are also at very high risk for CVD. In contrast to some earlier concerns, regarding the use of smoking cessation aids in smokers with mental disease due to a possible increase in psychiatric side effects, the multinational EAGLES trial found that nicotine patch, varenicline and bupropion were safe and effective in patients with stable psychiatric diseases.(66) Smoking quit rates were somewhat lower in smokers with psychiatric disease, suggesting that more intensive behavioral support may be needed in this group of CVD patients.

Hospitalization, particularly for acute coronary disease or other smoking-induced disease, is a good opportunity to discuss the importance of smoking cessation and initiate a quit attempt, since patients

may be more motivated to quit shortly after a CVD-related event and the hospital offers a smoke-free environment.(64, 71) In the hospital setting, nicotine replacement therapy should be initiated to reduce withdrawal symptoms, which can complicate disease management. Smoking cessation counseling should be initiated in the hospital, including planning for smoking cessation follow-up after discharge. Other smoking cessation medications such as varenicline can be started either during hospital stay or at/after discharge.(62, 64, 71) Following intensive smoking cessation counseling in the hospital, outpatient counseling (by telephone or in person) over at least one month can increase long term quit rates.(72) The use of automated interactive voice counseling at regular intervals has proven to be a successful and cost-effective approach to counseling after discharge.(73, 74)

8. PROGNOSIS

Quitting smoking rapidly and substantially reduces CVD-related and other health risks both in healthy smokers and smokers with CVD. (75, 76) Quitting smoking before the age of 50 halves the risk of dying in the next 15 years compared to continuing smoking, while the smoking-related increased risk of CHD is halved about 1 year after quitting, with a further gradual decline afterwards and a similar risk to nonsmokers after 15 years.(76) In patients with CHD, quitting smoking decreases the mortality risk by approximately 30%, which is higher than the reported reduction associated with other preventive measures such as e.g. antiplatelet therapy.(75, 77) The difference in absolute rates for major CVD events between smokers and ex-smokers in pooled analyses has been found to be more than twice the difference between high- and moderate-dose statin therapy.(78) Six months following an acute coronary syndrome event, quitting smoking was associated with a more than 40% reduction in risk of a repeat myocardial infarction compared to continuing smoking.(79) In patients with left ventricular dysfunction after a myocardial infarction, quitting smoking was associated with a lower hazard of all-cause mortality (approximately 40%) and death or a repeat myocardial infarction or death or heart failure hospitalization (approximately 30%). (80) These studies make clear that smoking cessation should be a priority among smokers with CVD and should be approached with the same intensity as other secondary preventive interventions.

9. NEWER DEVELOPMENTS IN TREATMENT

We focus on three particular developments that we believe hold promise for the treatment of CVD patients.

a. Pre-cessation Pharmacotherapy

Many smokers understand that they need to quit smoking but are not prepared to do so immediately. Clinical trials with nicotine patches and varenicline have shown that initiating pharmacotherapy while a smoker is still smoking and counseling that it will be easier to quit over time, results in reduced smoking and beneficial effects on quitting.(81, 82) Pre-cessation nicotine exposure is thought to desensitize nicotinic receptors, while varenicline blocks nicotinic receptors such that smoking becomes less satisfying and therefore easier to quit. The clinician can therefore approach every smoker with the offer of treatment whether or not they are prepared to immediately make a quit attempt, just as every patient with hypertension or hyperlipidemia is offered pharmacotherapy to prevent future disease. In support of the plausibility of this approach is a trial of smokers with COPD in whom the use of varenicline for as long as they wanted and without setting a fixed quit date resulted in very high quit rates at 18 months.(83)

b. ENDS and Nicotine harm reduction

There has been much debate about a potential role of e-cigarettes and heat-not-burn devices in smoking cessation, including among patients with CVD. There is compelling evidence that e-cigarettes can promote smoking cessation(84), although we are unaware of any published cessation trials in smokers with CVD. As discussed earlier in this paper, there are potential cardiovascular risks from nicotine and various thermal degradation products generated by ENDS, but it is highly likely that the risk is much less than that of combusted tobacco. We support a statement from an American Heart Association position paper regarding e-cigarettes: "If a patient has failed initial treatment, has been intolerant or refuses to use conventional smoking cessation medications, and wishes to use e-cigarettes to aid quitting, it is reasonable to support the attempt".(85) Other nicotine products such as low nitrosamine smokeless tobacco or the newer oral nicotine products have also been discussed as approaches to nicotine harm reduction, but evidence of effectiveness in promoting smoking cessation is not yet available.

c. Newer Medications

While pharmacotherapy is effective at promoting smoking cessation, the quit rates in clinical trials as well as in real-life setting remain relatively low, consistent with the relapsing nature of addictive behaviors. Another issue is access to pharmacotherapy, which may be limited due to financial or availability reasons in different parts of the world. Cytisine is a plant alkaloid that has nicotine like effects, while at the same time blocking the effects of nicotine, similar to varenicline.(86) Clinical trials show efficacy comparable with other first line smoking cessation medications, with relatively few adverse effects.(87-89) This drug is licensed in Eastern Europe, but not in the United States or in many other countries. Cytisine may be a particularly cost-effective way to treat smokers with CVD.

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DATA SHARING

No novel data sets were generated for this review. All included information was obtained from previously published reports.

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Table 1. Cardiovascular disorders caused by cigarette smoking

Vascular Disease
Accelerated atherosclerosis
Acute Myocardial Infarction
Shorter exercise time to angina
Coronary Spasm
Stroke
Aortic aneurysm
Peripheral obstructive arterial disease
Stent thrombosis after PCI
Graft occlusion after coronary bypass surgery
Arrhythmias
Sudden Cardiac Death
Atrial Fibrillation
Implantable defibrillator shocks
Myocardial Disease
Increases risk and aggravation of heart failure
hypertensive heart disease
Inducing Cardiac Risk Factors
Diabetes, type 2
Dyslipidemia
Hypertension, including malignant hypertension
Hypertensive renal disease
Others
Impaired wound healing
Erectile dysfunction
Reproductive disorders
Macular degeneration

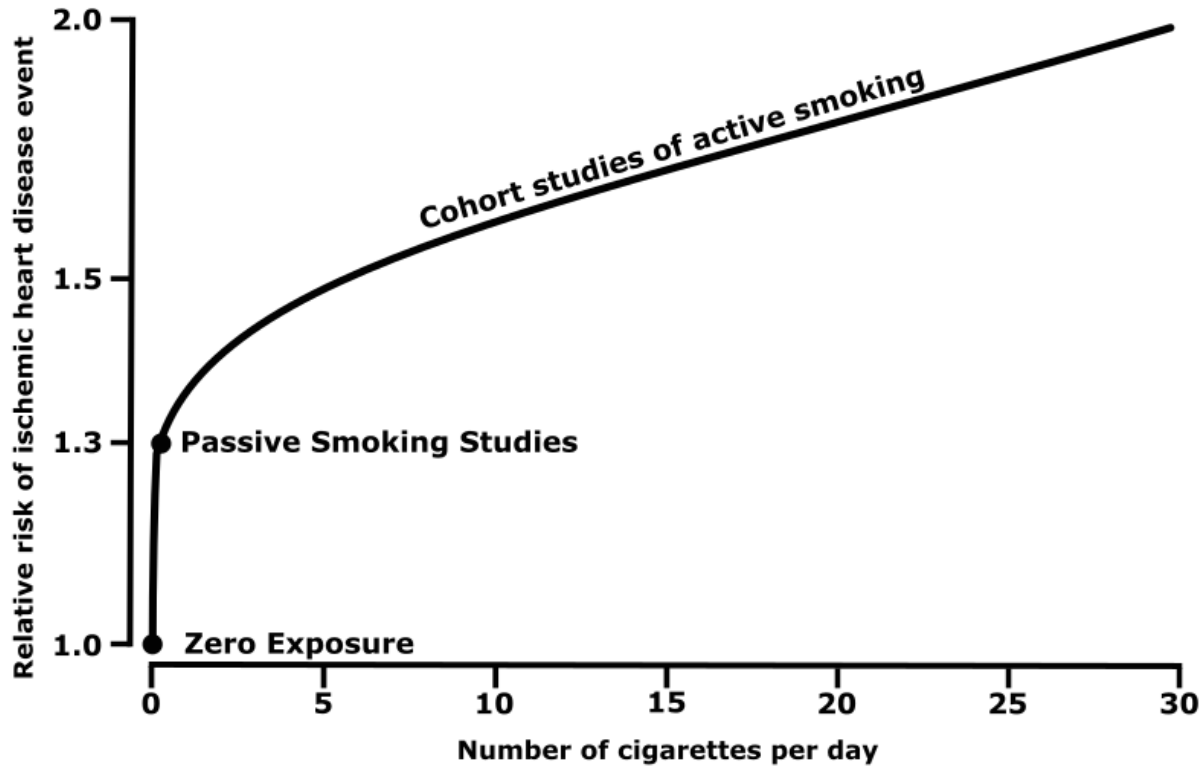

Figure 1. The dose-response relationship between cigarette smoking and risk for ischemic heart disease events

Summary estimate from the studies of environmental tobacco smoke exposure (taken to be equivalent to actively smoking 0.2 cigarettes per day). Adapted from Law and Wald, 2003 (6)

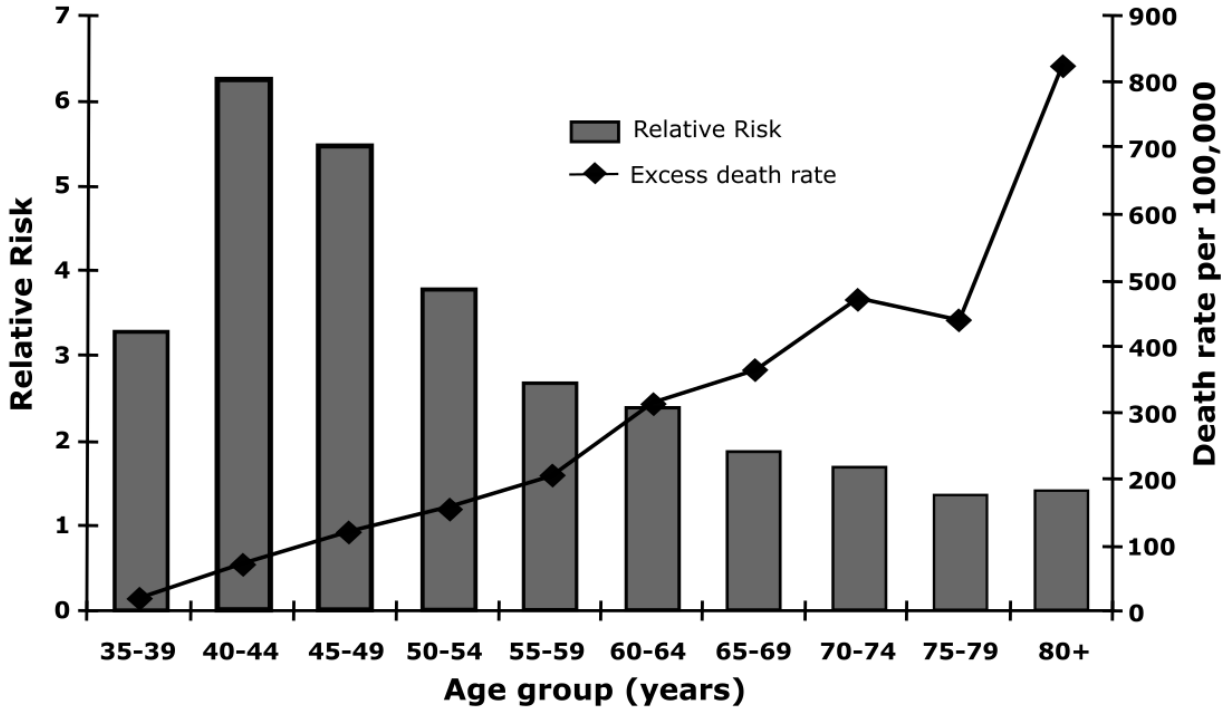

Figure 2. Relative risk and excess death rate for coronary heart disease for smokers compared to non-smokers, by age group

Data from American Cancer Society's Cancer Prevention Study II. Burns et al., 2003 (8)

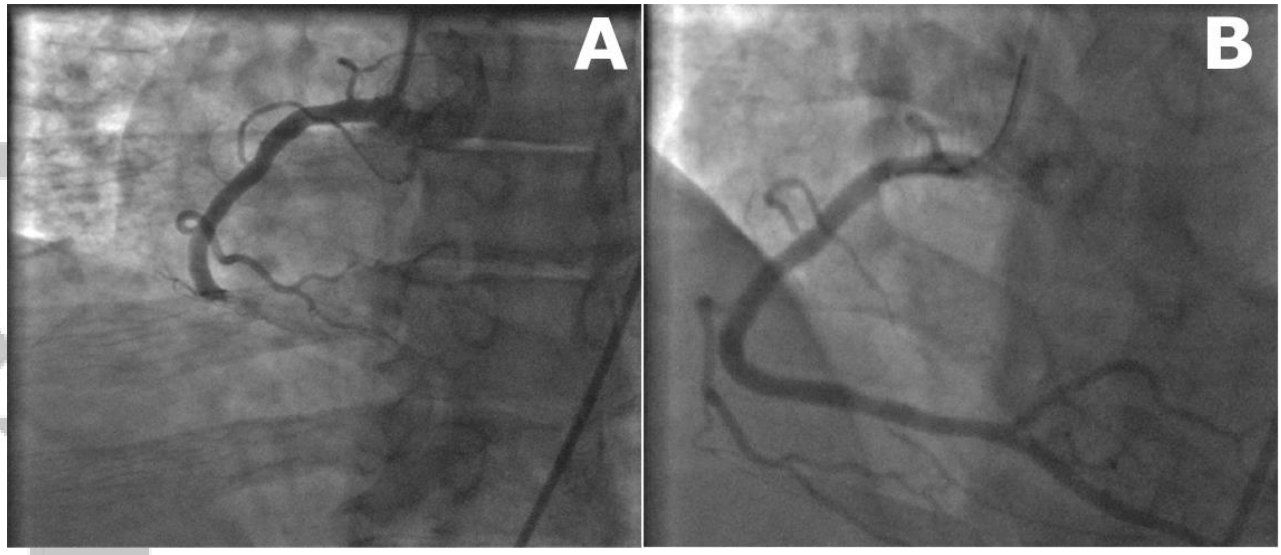

Figure 3: Thrombosis and myocardial infarction in smokers

Coronary angiograms from a 40-year-old male smoker hospitalized with acute myocardial infarction. Panel A shows a total obstruction of the right coronary artery. Panel B after thrombolysis shows minimal underlying atherosclerosis, demonstrating that thrombosis related to smoking can occur without significant underlying coronary artery disease. This phenomenon explains in part the "smoker's paradox", meaning that a smoker who quits smoking after a myocardial infarction has a better long-term prognosis than a non-smoker does. Photos courtesy of Dr. John MacGregor, Zuckerberg San Francisco General Hospital.

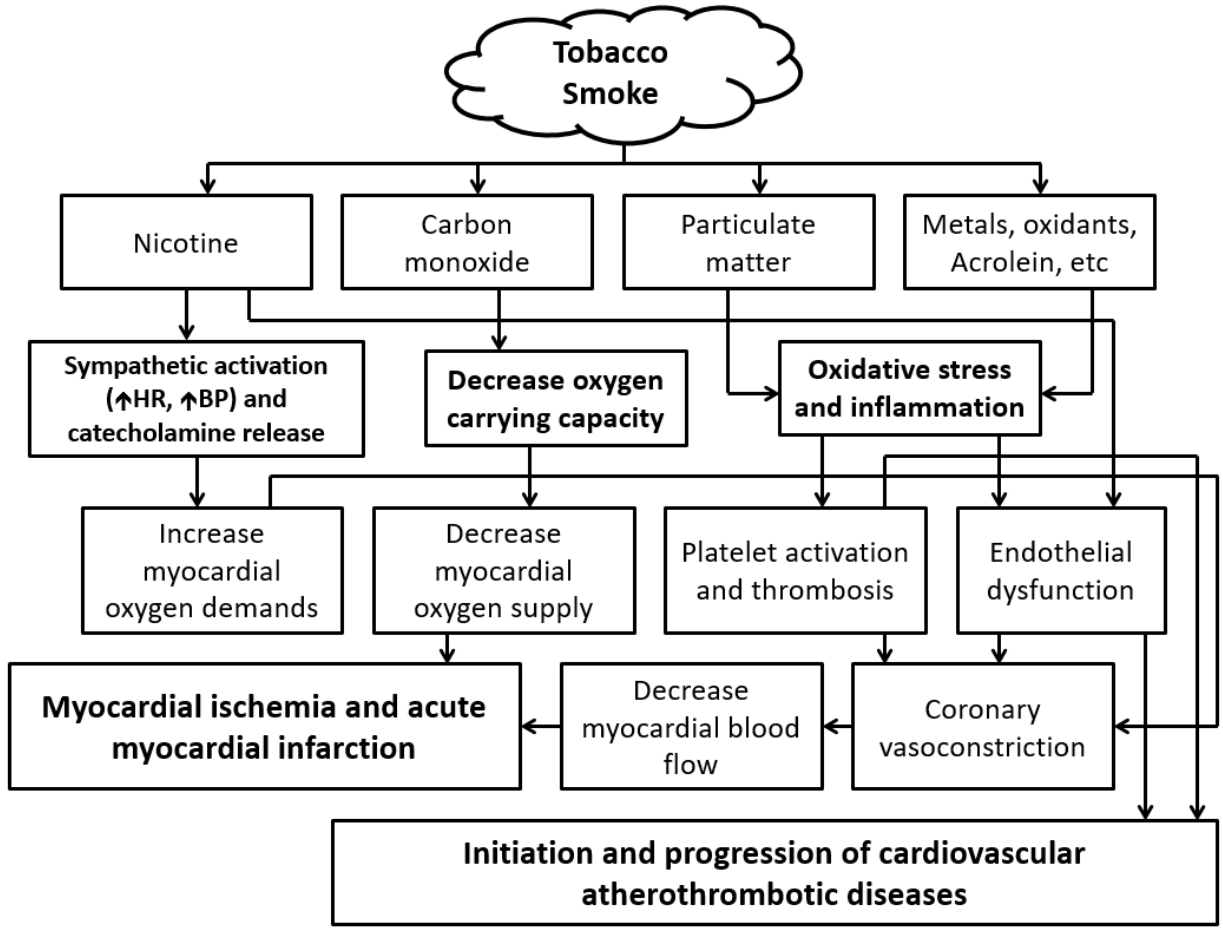

Figure 4: Potential mechanisms for tobacco smoke-mediated cardiovascular disease.

The flow diagram represents the probable central mechanisms underpinning tobacco smoke-mediated cardiovascular disease. Adapted from Rezk-Hanna and Benowitz, 2019 (35)