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Impact of tobacco smoking and smoking cessation on cardiovascular risk and disease

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Despite declines in smoking prevalence in many Western countries, tobacco use continues to grow in global importance as a leading preventable cause of cardiovascular disease. Tobacco smoke is both prothrombotic and atherogenic, increasing the risks of acute myocardial infarction, sudden cardiac death, stroke, aortic aneurysm and peripheral vascular disease. Even very low doses of exposure increase the risk of acute myocardial infarction. However, smoking cessation and second-hand smoke avoidance swiftly reduce this risk. While promising new agents are emerging, proven cost-effective and safe cessation interventions already exist, such as brief physician advice, counseling and nicotine replacement therapy. These should be routinely offered, where available, to all smokers. This is especially important for those at risk of, or with established and even acute, cardiovascular disease. Clinicians must play a more active role than ever before in supporting complete cessation in patients who smoke and in advocating for stronger tobacco control measures.

KEYWORDS: cardiovascular disease • cessation • risk • smoking • tobacco • treatment

Tobacco smoking is arguably the most important preventable cause of cardiovascular disease [1,2]. In the year 2000, 1.62 million deaths – more than one in every ten cardiovascular deaths in the world – were attributable to tobacco smoking, with 1.17 million of these among men and 450,000 among women [1]. Coronary heart disease accounted for 54% of smoking-attributable cardiovascular mortality, followed by cerebrovascular disease (25%), although there is regional variation in the role of smoking as a cause of various cardiovascular diseases [1,2]. In the USA alone, smoking is estimated to cause around 140,000 premature deaths from cardiovascular disease annually [2].

Prospects for improvement in this picture are not encouraging. Of the predicted 1 billion tobacco-related deaths in the 21st Century, 30–45% will be due to the cardiovascular effects of smoking [2]. Many of these premature deaths will occur in Asia, where the majority (53%) of the world's 1.1 billion smokers currently reside and where the prevalence of smoking is increasing, in contrast to a stable or declining prevalence in most of the developed world [3].

In light of the ongoing toll from tobacco smoking in the West, and the impending epidemic of cardiovascular disease in low- and middle-income countries, efforts to address tobacco-related harm need to be redoubled. Fortunately, an unprecedented investment of philanthropic funding is being directed towards initiatives that will support the early adoption of the components of the Framework Convention for Tobacco Control (FCTC) in growing economies such as China, Brazil and India. Most recently, the WHO has launched the MPOWER strategy for global tobacco control [4], a key element of which is treatment to help smokers stop smoking. This paper reviews the current evidence for the links between tobacco smoking and cardiovascular disease, identifies the cardiovascular benefits of smoking cessation, and summarizes current best practice and future directions in cessation of smoking treatment. In line with the renewed mandate from the WHO, it argues for a far more active role for clinicians in both treating patients and advocating for stronger tobacco control measures, locally and globally, than has been the case to date.

Association between smoking & cardiovascular disease

The association between smoking and cardiovascular disease was first elucidated in large epidemiological studies, in particular the British Doctors Study [5] and the Framingham Heart Study [6]. Although not given as much prominence as respiratory diseases at the time, smoking and its relationship to cardiovascular disease was one of the first topics addressed in the US Surgeon General's reports [7]. Subsequently, a large number of other epidemiological, clinical and laboratory studies in a range of settings among different population groups have provided consistent and compelling evidence of the leading role of tobacco smoking in the genesis of both acute cardiovascular events and atherosclerotic disease. In this section we review current epidemiological and pathophysiological evidence linking smoking with cardiovascular disease.

Epidemiology

Smoking has a greater impact on acute, typically thrombotic, events than on atherogenesis [8]. This is most marked in young and middle-aged adults, where smoking is responsible for approximately 50% of premature acute myocardial infarctions (AMIs) [8]. The relative risk (RR) of cardiovascular events is much greater in younger than in older smokers [9] principally because such events are extremely rare in young nonsmokers. In the INTERHEART study, a multicenter, case-control study conducted in more than 50 countries, Teo *et al.* compared 12,133 cases of first AMI with 14,435 age- and sex-matched controls, and found that the effect of current smoking was significantly greater in younger (odds ratio [OR]: 3.53; 95% confidence interval [CI]: 3.23–3.86) than in older participants (OR: 2.55; 95% CI: 2.35–2.76) and was especially marked in younger subjects who smoked 20 cigarettes or more per day, in whom ORs were 5.6 (95% CI: 5.1–6.2) [9]. However, the absolute excess mortality caused by smoking rises progressively with age [10].

Among people with an AMI, smokers have better short-term survival, a phenomenon known as the 'smoker's paradox' that exists presumably because these patients are younger, with few other risk factors and therefore with healthier coronary vessels than older nonsmokers [11]. While this unique combination of a greater propensity to acute thrombosis with less extensive atherosclerosis may confer a survival advantage over nonsmokers, smokers have worse outcomes than nonsmokers in other less acute coronary settings, such as after bypass surgery.

Tobacco smoking interacts in a multiplicative manner with the other major cardiovascular risk factors. When smoking is present with another risk factor, a higher risk generally results than would have resulted from simply adding together the independent risks [11]. For example, in a recent pooled analysis of 41 cohort studies involving over half a million participants (82% of whom were Asian), Nakamura and colleagues demonstrated that smoking significantly exacerbated the contribution of systolic blood pressure to the risk of hemorrhagic stroke. However, this was not found to be the case for ischemic stroke or coronary heart disease [12].

In general, cardiovascular risks increase with the number of cigarettes smoked each day [10,13], but the relationship is not straightforward. First, the measure of exposure widely used in studies – cigarettes per day – is of questionable validity. Smokers may smoke fewer cigarettes yet, in order to maintain their plasma nicotine level, may inhale more deeply, thereby increasing their exposure to harmful tobacco smoke toxins. Second, the type of tobacco product may misrepresent exposure. For example, 'low tar' and 'low nicotine' cigarettes are smoked differently from regular cigarettes [14] and, while cigar smoke contains the same toxins found in cigarette smoke, cigar smokers tend not to inhale [15,16]. Third, the association of smoking with cardiovascular risk is nonlinear. Smoking at very low levels of exposure (as low as 1–4 cigarettes per day) confers an almost threefold higher risk of dying from coronary heart disease compared with not smoking [13,17,18]. From five or more cigarettes per day the gradient of the exposure–risk curve is far less steep [19].

Coronary heart disease

As noted, there is a threefold increase in the odds of having a nonfatal AMI in current smokers compared with nonsmokers, and an increased risk of sudden cardiac death. The INTERHEART study investigators found an OR of a nonfatal AMI in current smokers compared with nonsmokers of 2.95 (95% CI: 2.77–3.14) [10]. In the British Regional Heart Study, Wannamethee *et al.* followed 7735 British men, aged 40–59 years, over 8 years and found that current smokers had more than double the risk of sudden cardiac death compared with nonsmokers (RR: 2.3; 95% CI: 1.2–4.0) [20]. Hasdai *et al.* followed-up 6600 patients who underwent percutaneous coronary revascularization from 1979 to 1995 for up to 16 years and found that current smokers had twice the risk of Q-wave infarction than nonsmokers (RR: 2.08; 95% CI: 1.16–3.72) [21].

Peripheral vascular disease

Peripheral vascular disease (PVD) affects approximately 20% of adults older than 55 years of age, roughly half of whom are asymptomatic. Of these, 5–10% progress to symptomatic PVD within 5 years. Cigarette smoking increases the risk of PVD sevenfold [22] and progression to symptomatic disease occurs a decade earlier than in nonsmokers. The risk of developing claudication increases with the intensity of smoking. The 5-year mortality for patients with claudication who continue to smoke is 40–50% [22–27]. Current smokers with PVD also have twice the amputation rate of nonsmokers [28], an increased risk of graft failure following femoro-popliteal bypass surgery [29] and increased postoperative mortality [30].

Abdominal aortic aneurysm

Smoking is the most important modifiable risk factor for development of abdominal aortic aneurysm (AAA) and not only

leads to progression of aortic atherosclerosis, but also increases the risk of AAA formation [31] and expansion [32]. Reported RRs of AAA associated with cigarette smoking in the literature range from 2 to 9 and a dose–response association has been found. For example, in a UK study of 5356 men and women followed between 1988 and 1995, the level of risk for AAA increased with the number of cigarettes smoked daily [33]. In a systematic review, Lederle *et al.* noted that in men the association of current smoking with AAA was 2.5-times greater than the association with coronary artery disease and 3.5-times greater than with cerebrovascular disease [34]. In the largest cohort study of AAA to date, more than 100,000 people were followed for a median of 13 years and up to 33 years for the outcome of incident – clinically apparent AAA [35]. Cigarette smoking of three or more packs per day was the strongest risk factor for incident AAA in this cohort (RR: 6.6), followed by age 65 years or older (RR: 6). The results confirmed the previously reported associations with smoking and showed a dose–response association with adjusted RRs of 3, 5 and 7 for current smokers of less than one pack per day, between one and two packs per day, and of three or more packs per day, respectively [35].

Stroke

Smoking is a risk factor for ischemic stroke, hemorrhagic stroke and subarachnoid hemorrhage in both men and women [36] and increases the risk of mortality from stroke, although the dose-related increase seen in women is not as pronounced as in men [37]. In the Nurses' Health Study, Colditz *et al.* evaluated more than 118,539 US women aged 30–55 years for 8 years (1976–1984) and found that current smokers had a significantly higher rate of stroke, both nonfatal and fatal, and the risk of stroke increased with the number of cigarettes smoked daily [38]. More recently, Kelly and colleagues investigated the relationship between smoking and stroke incidence and mortality in a cohort study involving almost 170,000 Chinese men and women aged 40 years and over, followed for an average of 8.3 years [39]. The RRs of stroke and stroke mortality associated with current smoking compared with ever smoking were 1.28 (95% CI: 1.19–1.37) and 1.13 (95% CI: 1.03–1.25) in men and 1.25 (95% CI: 1.13–1.37) and 1.19 (95% CI: 1.04–1.36) in women, respectively, and there appeared to be a dose–response relationship with the number of cigarettes smoked per day and with duration of smoking. Smoking also potentiates the effects of other stroke risk factors, such as oral contraceptive use [40].

Pathophysiology

Cigarette smoke is a complex mix of more than 4000 chemicals [41], including polycyclic aromatic hydrocarbons and oxidant gases that are known to be cardiotoxins. However, the nature and relative toxicity of many of these chemicals is still poorly understood [42]. It is not surprising, therefore, that the

pathways linking smoking with cardiovascular disease have not yet been fully elucidated. As understanding of these complex mechanisms and their relative importance increases, so too does the prospect of developing new approaches to prevention and treatment. We first consider the role of nicotine, as it can perhaps lay claim to being the most well-known, but also the most misunderstood, constituent of cigarette smoke.

Nicotine

Nicotine is a sympathomimetic chemical that promotes the release of catecholamines and other neurotransmitters acting centrally and peripherally. In addition to its cardiovascular effects such as elevated heart rate, blood pressure and cardiac output [42], nicotine has metabolic effects, in particular increased lipolysis. Lipolysis leads to increased levels of circulating free fatty acids and glycerol in the blood and the resulting increase in fat metabolism drives a demand for more oxygen, leading to increased coronary blood flow and myocardial oxygen uptake [43]. Inhaled nicotine from cigarette smoke is delivered rapidly in high concentrations in the arterial blood to the heart. The rapidity of absorption and the peak arterial blood concentrations are determinants of the magnitude of at least some of the cardiovascular effects of nicotine. In healthy smokers, these cardiovascular and metabolic effects are unlikely to be hazardous. However, in people with established coronary artery disease there is a theoretical increase in risk of a cardiac event since, unlike exercise-induced sympathetic activity, nicotine-induced sympathetic activity leads to greater myocardial oxygen demand without a concomitant increase in organ blood flow and with an increase in vasoconstriction, including constriction of the coronary vessels disease [43]. These effects could potentially trigger symptoms of ischemia in such smokers. One might also expect that the hemodynamic effects of nicotine would contribute to endothelial damage and accelerate the progression of atherosclerosis [44].

In fact, the clinical evidence does not support a major role for nicotine in cardiovascular disease. Studies of smokeless tobacco users shed some light. Smokeless tobacco users absorb the same amount of nicotine as cigarette smokers, but are not exposed to tobacco combustion products. Nicotine absorbed from cigarette smoke is more rapidly absorbed and rapidly attains peak arterial concentrations compared with nicotine absorbed slowly from smokeless tobacco, given an equivalent daily exposure. However, smokeless tobacco produces sympathomimetic effects similar to those produced by smoked tobacco [45,46]. The key difference is that smokeless tobacco does not lead to the inflammatory reaction seen in smokers, nor does it produce the endothelial dysfunction, platelet activation or evidence of oxidant stress believed to be fundamental to pathogenesis [47]. Rather, it is the other constituents of cigarette smoke that are responsible for the prothrombotic and atherogenic changes underlying cardiovascular disease. The contribution of nicotine to aggravating myocardial ischemia, smoking-related atherosclerosis and cardiovascular disease is of little clinical importance [48,49]. The crucial role that nicotine

plays in cardiovascular disease is in initiating and maintaining tobacco dependence, thereby exposing smokers to the other far more hazardous components of tobacco smoke [43].

Carbon monoxide

Another constituent of cigarette smoke implicated in the pathway from smoking to cardiovascular disease is carbon monoxide (CO) [48]. Inhaled CO binds swiftly to hemoglobin, reducing not only oxygen-carrying capacity but also inhibiting oxygen release from hemoglobin that is not directly bound to CO. Carboxy-hemoglobin levels in smokers average 5%, but may be as high as 10%, compared with levels of only 0.5–2% in nonsmokers. The resulting relative hypoxemia leads to a compensatory increase in red cell mass and in blood viscosity. CO may also increase the occurrence of ventricular arrhythmias. Early studies reporting evidence of direct effects of CO on atherosclerosis and thrombus formation have not been confirmed by more recent work [43].

The most important mechanism implicated in initiating acute cardiovascular events is the development of a hypercoagulable state leading to thrombosis [50]. Epidemiologic studies indicate that cigarette smoking increases the risk of AMI and sudden cardiac death, mediated by thrombosis, much more than it increases the risk of angina pectoris, which is caused primarily by hemodynamic factors [50]. Cigarette smoking contributes to thrombosis by promoting platelet activation and aggregation and through stimulating prothrombotic changes in clotting factors [51]. Levels of circulating fibrinogen, one of the strongest predictors of coronary events, are increased in smokers [52,53]. Increases in fibrinogen levels act in tandem with the increased red cell mass from long-term CO exposure, increasing blood viscosity and enhancing platelet activation, which, in turn, promotes atherogenesis [53,54]. Fibrinogen may also contribute to atherosclerosis through a direct effect on platelets [54]. Tissue factor (TF), another link in the chain, is present in atherosclerotic plaques and may promote plaque thrombogenicity and possibly thrombus propagation where there is existing atherosclerosis [55]. Sambola *et al.* found that smoking increases plasma levels of TF in smokers who smoke ten cigarettes or more per day with a smoking history of 10 or more years, within 2 h after smoking just two cigarettes [55].

Oxidant gases

Oxidative stress, the oxidation of lipids, proteins and DNA leading to cellular damage, is now known to be a pivotal factor in atherogenesis [8,43]. It occurs when there is an imbalance between production of oxidants and endogenous protective antioxidants, such as nitric oxide (NO), a key factor in regulating normal vascular tone [56]. Cigarette smoke is not only a rich source of oxidant chemicals, such as hydrogen peroxide, peroxynitrite and superoxide [56], but also stimulates the generation of oxidants *in vivo* [56]. Furthermore, oxidant chemicals increase the destruction of 'protective' antioxidants in smokers, but this is reversible with administration of antioxidants such as vitamin C [57]. Antioxidants have been shown to reverse endothelial dysfunction [58], and reduce inflammation [59] and

other adverse changes associated with cigarette smoking [60–62]. Oxidation of LDL may also promote atherosclerosis. Smokers have higher levels of oxidized LDL, which is taken up preferentially by macrophages, a pivotal step in the development of foam cells that are found in atherosclerotic lesions [63,64].

Oxidants in cigarette smoke also decrease NO release and bioavailability [56]. Barua *et al.* took serum from nonsmokers and current smokers who had abstained from smoking for a 6–8-h period and incubated it with human umbilical vein endothelial cells (HUVECs). After 12 h, HUVECs incubated with current smoker's serum showed significantly lower basal NO production compared with HUVECs incubated with nonsmoker's serum, suggesting that smoking is associated with reduced basal NO production [65]. Celermajer *et al.* found a significant association of cigarette smoking with impaired endothelium-dependent vasodilation of different blood vessels, one of the earliest effects of the various risk factors for atherosclerosis [66]. This occurs before changes in the blood vessel walls are evident and appears to be a consequence of smoking-induced impairment of endothelial NO release [67,68]. NO also plays a role in regulating platelet activation and recruitment into aggregates and at normal levels inhibits smooth muscle cell proliferation and adhesion of monocytes to the endothelium. Thus, the impaired endogenous NO release seen in smokers may contribute to both acute cardiovascular events and accelerated atherogenesis [67,68].

Smoking also promotes a chronic inflammatory state. Cigarette smoking is consistently associated with increased circulating neutrophil counts [69]. For example, Lavi *et al.* found that current smokers with no evidence of coronary artery disease have significantly increased white blood cell counts compared with nonsmokers [70]. Epidemiological studies have shown that elevated white blood cell counts are associated with a greater long-term cardiovascular risk [71,72]. Neutrophils may promote cardiovascular disease by releasing oxidant chemicals, proteases and leukotrienes [73] that, in turn, cause endothelial cell injury and the aggregation and activation of platelets.

The effects of these complex interdependent pathphysiological processes are also evident in studies tracking the development of atherosclerosis in smokers and nonsmokers. Serial quantitative coronary arteriography has demonstrated that active smoking promotes the formation of new lesions and accelerates progression of existing coronary artery disease [74]; Howard *et al.* found active smoking to be associated with increased progression of carotid atherosclerosis, as assessed by carotid ultrasound to evaluate carotid intima–medial thickness, in over 10,000 participants [75].

Second-hand tobacco smoke exposure

In a comprehensive meta-analysis of ten cohort studies and eight case–control studies involving around half a million participants, He *et al.* found that second-hand smoke (SHS) exposure was

associated with a 25% increase in the risk of acquiring coronary heart disease and its sequelae [76]. SHS also contributes to the progression of atherosclerosis and is associated with increased infarct size in smokers who experience a myocardial infarction [77]. In their review of the literature on the association of SHS with cardiovascular disease, Law *et al.* found that nonsmokers exposed to smoke from smoking spouses experience on average a 30% excess risk of ischemic heart disease death and of non-fatal AMI [19]. SHS has also been implicated as a causal factor in stroke for males and females in several well-conducted epidemiological studies [78–81] but the association with duration and amount of exposure is unclear to date [81].

Second-hand smoke is largely derived from the side stream smoke of other's cigarettes and is qualitatively different from the mainstream smoke inhaled by smokers through their own cigarette. Side stream smoke is far more toxic, with concentrations of known toxins such as oxidant gases higher by several multiples than mainstream smoke [41]. Thus, the mechanisms of action are the same with SHS as those in active smoking but the effects are magnified out of proportion to exposure: despite an exposure to tobacco smoke of less than 1% of the exposure from smoking 20 cigarettes per day the excess risk is as much as a third of that of a smoker of 20 cigarettes per day [9].

The role of genes

As Benowitz has observed, if 50% of lifelong smokers die prematurely from smoking-related diseases then 50% of such smokers do not [8]. Some develop severe cardiovascular disease at an early age whereas others who have smoked for many years appear to be resistant. This variation may be explained not only by the presence and force of other risk factors for cardiovascular disease besides smoking but also to genetics. The review of the genetic influences of cigarette smoking-induced cardiovascular diseases by Wang *et al.* showed that genetic variants can indeed modify the development of atherosclerosis in smokers [82]. Polymorphisms (such as endothelial NO synthase polymorphisms) may increase susceptibility to coronary heart disease and AMI. However, it is difficult to assess their clinical importance since the prevalence of these variants in populations of smokers is as yet unknown [82].

Recently, researchers have begun to explore the genetic basis of nicotine dependence. Thorgeirsson *et al.* identified a common variant in the nicotinic acetylcholine receptor gene cluster on chromosome 15q24 with an effect on the number of cigarettes smoked per day, nicotine dependence and the risk of PVD in populations of European descent [83]. Lou *et al.* have found an association between GABA_A receptor-associated protein and *DLG4* with nicotine dependence in chromosome 17p13 of European-Americans [84]. In a large study targeting 348 candidate genes, Saccone *et al.* identified cholinergic nicotinic receptor genes that have an association with nicotine dependence [85]. Such studies are important but need replicating and their relevance to therapeutic interventions is as yet unclear.

Benefits of smoking cessation

Smoking cessation almost completely reverses the risk of cardiovascular disease from smoking, making it potentially the single most effective and lifesaving intervention available for those at risk of and with existing cardiovascular disease [10,86–90]. Cessation rapidly reduces the risk of cardiovascular events including fatal events. A recent analysis of the Nurses' Health Study found that women who quit smoking experienced a rapid decline in the risk of death from coronary heart disease and stroke, with 61% of the benefit of cessation on coronary heart disease death and 42% of the benefit on stroke death realized within 5 years after stopping smoking [91]. Lightwood and Glantz demonstrated that the decline in RR for AMI and stroke after smoking cessation follows an exponential decay curve [92]. The curve flattens out within 4 years after quitting but the RR remains above 1.0 and is higher for stroke than for AMI [92]. This suggests that the benefits of cessation begin to be realized almost immediately a smoker quits [10], as one might expect from the pathophysiological mechanisms at play. For example, within just 2 weeks of cessation by former long-term smokers, both fibrinogen concentration and the rate of fibrinogen synthesis are reduced [93]. There is reduced platelet volume [94] and platelet aggregability [95]. A significant reduction in white blood cells occurs [96] and a more favorable lipid profile begins to develop, with an increase in HDL, an increase in the HDL/LDL ratio, and a decrease in LDL [96,97]. Hemodynamic parameters also change in a favorable direction: significant reductions occur in mean arterial pressure, heart rate and arterial compliance [98].

Cessation is especially effective for those with established cardiovascular disease. Benefits occur for all age groups and among patients with previous AMI and stroke and patients who have undergone revascularization procedures: a recent systematic review provided strong evidence that quitting smoking after AMI or cardiac surgery can decrease a person's risk of death by at least a third [86]. The beneficial impact of quitting smoking after serious heart disease may be as great or greater than other possible interventions and the risk reductions are consistent, regardless of differences between studies in index cardiac events – age, sex, country and time period [86]. The risk of sudden cardiac death also falls swiftly, within hours. The risk of AMI is significantly reduced within a few years of quitting [10]. Cessation also reduces arrhythmic death for patients with post-AMI left ventricular dysfunction [87] and significantly reduces the risk of recurrent cardiac arrest [88].

Other vascular beds also benefit. Smokers with intermittent claudication who stop smoking demonstrate reductions in PVD progression. In a Swedish study that followed 343 patients with claudication over 7 years, rest pain developed in 26 patients, all of whom were current smokers, while none of the ex-smokers developed rest pain [89]. Compared with current smokers, male ex-smokers have a reduced risk of nonfatal stroke. Robbins *et al.* prospectively evaluated 22,071 male physicians in the Physicians' Health Study and, after adjusting for age and treatment assignment, found that physicians who were ex-smokers had a lower

RR of total nonfatal stroke (RR: 1.2; 95% CI: 0.95–1.63) than physicians currently smoking less than 20 and more than 20 cigarettes daily, (RR: 2.0; 95% CI: 1.04–3.33 and RR: 2.5; 95% CI: 1.84–3.98 respectively [90].

As noted earlier, the RR of cardiovascular events is much greater in younger versus older smokers, primarily because cardiovascular events are rare in young nonsmokers [10]. Although the RRs decline considerably with age, the absolute excess mortality caused by smoking rises progressively with age. Therefore, it is important for clinicians to promote smoking cessation even in elderly smokers.

Smoking cessation in patients with cardiovascular disease

While cessation is an important disease-prevention strategy in smokers without established cardiovascular disease, smoking cessation in patients with known disease should be accorded the highest priority. Complete cessation of smoking offers the single best opportunity for improving cardiovascular health. As this review has highlighted, merely cutting down may not be sufficient to protect from acute cardiovascular events [99].

Cessation is also more cost effective than any other preventive cardiology measure. For example, Lightwood estimated the cost for the typical treatment regimen of nicotine replacement therapy, providing gum or patch, and brief physician counseling to be in the range of US\$2000–6000 per life-year saved compared with no treatment [100]. This compares very favourably with an estimated US\$9000–26,000 cost per life-year saved for the treatment of moderate-to-severe hypertension, or US\$50,000–196,000 for the treatment of hyperlipidemia in primary prevention [101].

Unfortunately smoking cessation is not part of routine practice for many physicians. Tobacco smoking may be regarded simply as a 'bad habit' or a 'lifestyle choice' and not as a disorder of dependence requiring treatment. Clinicians may lack confidence in even asking patients if they smoke, let alone treating smokers, because they have not been trained to do so [102], or they may claim to have insufficient time.

Without doubt, providing smoking cessation treatment is not easy. Tobacco dependence is a chronic relapsing condition and usually requires repeated interventions, including both pharmacotherapy and counseling, before successful long-term abstinence is achieved [10]. Many patients with cardiovascular disease are highly nicotine dependent, as evidenced by low quit rates seen in most studies of smoking cessation in such patients, even after major cardiovascular interventions [103]. Nevertheless, cardiovascular patients identified as smokers should be offered the most intensive smoking cessation interventions feasible at every visit or admission, including both counseling and pharmacotherapy.

Another argument that can be mounted for treating tobacco dependence quite aggressively in this population is that smoking can affect the action of other cardiovascular medications. For example, it speeds up the metabolism of flecanide and

propranolol [104,105] and may lead to a poorer blood pressure response to nonselective β -blockers because of its combined α - and β -adrenergic agonist effects.

The pathophysiology of smoking-induced cardiovascular disease is useful to consider when treating smokers with established cardiovascular disease. For example, treatments that improve endothelial function (such as lipid-lowering drugs and excellent diabetes control) are likely to be especially beneficial in smokers. One might expect that antioxidants could also offer benefit. However, there is mixed epidemiologic evidence as to whether antioxidants protect against coronary heart disease [106,107]. A recent meta-analysis showed no evidence of benefit in preventing or treating patients with cardiovascular disease with antioxidants [108], but the effect on smokers in particular has not yet been studied. In smokers with AMI one might expect that thrombolysis would be a better option than angioplasty. However, the results of both types of intervention appear to be similar in smokers [8]. Where a smoker who has had an AMI does not quit despite every effort, anticoagulant therapy such as long-term warfarin therapy may be beneficial, in addition to standard aspirin treatment, although there are as yet no empirical data to support this recommendation [8]. Smokers who continue to smoke following percutaneous coronary revascularization or coronary artery bypass graft surgery have a higher likelihood of re-occlusion after AMI and an increased risk of recurrent ischemia [109]. In this group, prolonged anticoagulation and lipid lowering may be even more important than in nonsmokers [8].

Brief advice

The evidence for a wide-range of cessation interventions has recently been reviewed and summarized in the 2008 update of the US cessation guidelines, *Treating Tobacco Use and Dependence* [110]. At a minimum, busy clinicians can provide brief advice – as brief as half a minute – to stop smoking. Brief advice from a physician can prompt quit attempts in up to 40% of patients and substantially increases the probability of success (by approximately 2.5%) [110,111]. Nursing staff can reinforce these messages and provide more support and follow-up counseling [110–112]. Referral to other support services including telephone quitlines (see later) can be made.

Pharmacotherapy

Recent advances have occurred in the pharmacologic treatment of tobacco dependence, and numerous pharmacotherapies now exist [113]. The most widely used treatment is nicotine replacement therapy (NRT) but newer, highly targeted treatments, such as varenicline, are becoming more widely available.

Nicotine replacement therapy

Tobacco cessation typically causes nicotine withdrawal symptoms such as irritability, anxiety and hunger in many patients [114]. The use of pharmacotherapies, which provide direct nicotine replacement, is a logical approach to try to reduce these negative

effects. NRT is well-established in smoking cessation and includes a wide range of delivery systems including gum, transdermal patch, nasal spray, inhaler and lozenge [115]. However, none of the NRT products currently available delivers nicotine at the same speed or dose as delivered by cigarettes. Nevertheless, all NRT products are of proven and approximately equivalent efficacy, improving the likelihood of long-term abstinence compared with placebo by 50–170% (ORs range from 1.5 to 2.7) [110,115,116].

Nicotine replacement therapy is just as effective in patients with cardiovascular disease as in those without. Nevertheless, many clinicians have been reluctant to provide NRT to such patients because of concerns over safety [117]. This fear should now be put to rest once and for all. Using any form of NRT, including combinations such as patch and gum, or patch and nasal spray, is far safer than continued smoking. The risks, even for those with severe cardiovascular disease, are small and are far outweighed by the benefits of smoking cessation [48]. As discussed, nicotine has known cardiovascular effects but clinical trials of NRT in patients with underlying, stable coronary disease indicate that NRT does not increase cardiovascular risk [117]. Even when NRT is used while still smoking, the effects are similar to those of cigarette smoking alone because the dose–cardiovascular response curve for nicotine is flat [117].

In situations where patients are acutely ill, oral, shorter-acting forms of NRT (gum or lozenge, for example) have often been favoured by clinicians in preference to transdermal patches. The rationale has been that in the event of a crisis, nicotine levels are able to reduce more rapidly [118]. However, a recent study of smokers with acute coronary syndrome who received patches found no increase in short- or long-term mortality compared with a matched sample who did not use patches [119]. On this basis, NRT should be offered to all smokers with cardiovascular disease [117] with only very few provisos and precautions (Box 1) [117,120,121,201]. These recommendations go further than the manufacturer's instructions, which tend to be very conservative.

Bupropion

Bupropion, initially promoted as an antidepressant treatment, was the first non-NRT treatment for smoking dependence shown to be effective. Bupropion doubles the likelihood of abstinence over placebo and is more effective than the nicotine patch [122]. Bupropion's efficacy in smoking cessation is unrelated to its antidepressant effects. While its precise mechanism of action is unknown, it is likely to be related to inhibition of dopamine and/or noradrenaline neural reuptake. The most common side effects are insomnia and dry mouth [123]. Bupropion appears to be safe in patients with cardiovascular disease [124], although dosage reduction may be needed when patients are taking Type 1c antiarrhythmics [125].

Varenicline

Varenicline is a partial agonist at the $\alpha 4\beta 2$ nicotinic acetylcholine receptor, where the dependency-causing properties of nicotine are mediated [126]. As a partial agonist, varenicline relieves withdrawal

Box 1. Using nicotine replacement therapy in patients with cardiovascular disease.

- In stable cardiovascular disease, NRT presents a lesser hazard than continuing to smoke and is safe to be used *ad libitum* as needed.
- NRT should be considered in smokers hospitalized with a recent myocardial infarction, severe arrhythmia or recent cerebrovascular accident and/or who are considered to be hemodynamically unstable. However, initiation of treatment and determination of dose in these circumstances should be determined after obtaining medical advice.
- Any form of NRT that is acceptable to the patient and appropriate to the clinical context may be used.
- NRT should ideally be accompanied by ongoing behavioral support.

NRT: Nicotine-replacement therapy.

symptoms and cravings while, as an antagonist, it blocks the reinforcing effects of nicotine. Varenicline is more efficacious than both placebo and bupropion in clinical trials [125]. In a randomized, double-blind, placebo-controlled trial, the odds of quitting smoking with varenicline were significantly greater than the odds of quitting with either placebo (OR: 3.85) or slow-release bupropion (OR: 1.90) [126]. Varenicline has few interactions and appears to be safe to use in patients with cardiovascular disease [127,128]. However, recent reports of neuropsychiatric problems such as depressed mood, suicidal ideation, attempted or completed suicide, erratic behavior and agitation in some patients using varenicline for cessation may limit its use [129].

Other pharmacotherapies

Other less commonly used pharmacotherapies for smoking cessation include clonidine, nortryptiline, SSRI antidepressants and anxiolytics. There is insufficient evidence to support or refute the use of SSRIs and anxiolytics [130] but clonidine and nortryptiline are effective and relatively inexpensive. However, their role in smoking cessation is limited due to side effects [125,130] and there are precautions in patients with cardiovascular disease. Nortryptiline in particular should be avoided in patients with a recent AMI or arrhythmia [131].

Other treatments

Despite widespread promotion of their effectiveness, there is currently insufficient evidence to support most other treatments available for tobacco smoking dependence. In particular, there is little evidence to support the use of acupuncture or hypnosis in smoking cessation [132,133].

Second-hand smoke avoidance

'Natural experiments' in the USA and Italy, where the enactment of smokefree ordinances appears to have resulted in significant reductions in hospital admission rates for AMI, provide

evidence in support of these strategies [134–136]. Smokers and nonsmokers alike need to be alerted to the cardiovascular hazards of SHS exposure [137]. Individuals with existing cardiovascular disease are more susceptible and should be advised to avoid exposure to SHS if at all possible. Elimination of SHS exposure in public places, in the workplace and at home are vital if these risks are to be minimized.

Other support

Telephone quitlines have been shown to substantially increase quitting rates and are an option for the busy physician [138,139]. Mobile phone SMS messaging support also shows promise [140]. In hospitals and clinics, specialist cessation advisors can take referrals from busy clinicians and with the aid of systems changes (such as automated reminder messages on computers) and protocols, help ensure that every smoker is asked about their smoking, given brief advice to stop and offered ongoing support (pharmacotherapy and, if time allows, counseling) during their hospital or clinic visit and beyond discharge [141].

Expert commentary

The beneficial effects of smoking cessation in cardiovascular patients and those at-risk are now indisputable. Effective treatments exist but much more needs to be done to make them more widely available. For example, NRT should be made more affordable and widely available to prompt and support more quit attempts [142]. The German pathologist Rudolf Virchow, of Virchow's triad fame, asserted that 'physicians are the natural attorneys of the poor' [143]. Perhaps if he were still alive, Virchow would argue that physicians are also the 'natural attorneys' of the smoker. In the light of the alarming forecasts for the global tobacco epidemic, health professionals around the world must become more active at incorporating simple cessation support into their practice. Those who care for people with cardiovascular disease are ideally placed to be tobacco-control advocates: to actively support smoke-free hospitals and clinics, workplaces and public places, and to advocate for other tobacco control policies that have potential to benefit both individuals and populations [144]. Cessation treatment and tobacco control should also be integrated into the education curricula of physicians, nurses and allied health workers [144]. To neglect to provide advice, offer treatment and support to help smokers quit, and to fail to advocate for more aggressive tobacco control measures in the face of the overwhelming evidence for the benefits of cessation and avoidance of tobacco smoke exposure, may be seen as a failure by clinicians to provide best practice [145].

Five-year view

In 5 year's time, the demand for smoking cessation support will be far higher. Social attitudes towards tobacco smoking will have made smoking socially unacceptable in many

countries. The range of safe and effective pharmacotherapies available to clinicians will have expanded significantly. Nicotine delivery systems, such as the nicotine oral pouch and novel inhaler devices (such as the 'e-cigarette') that mimic more closely the speed and dose of nicotine delivery from cigarettes, will have emerged from the development pipeline. A wide range of nicotine delivery products will be widely available over the counter in retail outlets, hospitals, entertainment venues and airports without prescription. For heavily dependent smokers who simply cannot quit nicotine, a slow-release form such as in smokeless tobacco or nicotine patches will be available, with precautions, for use for long-term maintenance of nicotine addiction.

A growth in understanding of the neurobiology of drug-dependence mechanisms will continue to point the way to new targets for the pharmacotherapy of tobacco dependence, adding to the number of drugs that follow from varenicline. A handful of nicotine vaccines will also be available that stimulate the production of antibodies to nicotine and restrict the amount of nicotine penetrating the brain, thus reducing the psychopharmacological responses to nicotine and reducing dopamine turnover in the nucleus accumbens [146]. While well tolerated, the antibody levels generated by these vaccines vary widely from individual to individual and are short-lived, so this approach will assist some smokers to quit but will have only a limited role in the primary prevention of smoking dependence [147].

Other groups of agents likely to emerge from the development pipeline include those that interfere with the liver enzymes that metabolise nicotine, such as selegiline, a monoamine oxidase inhibitor used for the treatment of early-stage Parkinson's disease and senile dementia [148] and the next version of tetrahydrocannabinoid receptor blockers, the group to which rimonabant belongs, currently used for weight control but not licensed yet in the USA for cessation, despite evidence that it is effective [149]. Cytisine, the agent from which varenicline was developed, will have become widely available in lower-income countries [150].

While such novel therapies and delivery systems are important, and more work is clearly needed to develop these, the key treatment challenge for the immediate and near future is to encourage clinicians to be more active in asking their patients if they smoke, giving brief advice to stop smoking and using existing treatments already available that are of proven acceptability, efficacy and safety.

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Key issues

- Smoking is arguably the most important preventable cause of cardiovascular disease globally.
- Smoking acts synergistically with other cardiovascular risk factors to increase the risks of myocardial infarction, sudden cardiac death, stroke, peripheral vascular disease and aortic aneurysm.
- The pathophysiology of smoking-induced cardiovascular disease is complex but it now appears that oxidative stress induced by toxins in cigarette smoke plays the central role in the development of both smoking-induced thrombosis and atherosclerosis.
- Smoking cessation leads to an almost immediate reduction in the risks of cardiac events. Over time, most of the cardiovascular risk induced by tobacco smoking is reversible.
- Even small exposures to tobacco smoke can trigger acute cardiac events. Therefore, complete cessation and avoidance of second-hand smoke exposure is important, especially for patients with established disease.
- Smoking cessation treatments are safe in almost all circumstances, including in the context of acute cardiovascular disease events. They are also highly cost effective and can more than double the chances of a successful quit attempt.
- Physicians have a responsibility to ensure that every smoker under their care, in particular those at high risk of cardiovascular disease, receives appropriate cessation treatment and support.
- Physicians also have an important role as advocates for wider tobacco control initiatives that offer both individual and population benefits, such as legislation that promotes smoke-free workplace and recreational environments.

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