

ASH Research Report: Smoking & Peripheral Arterial Disease (PAD)

December 2017

WHAT IS PAD?

Peripheral arterial disease (PAD), also known as peripheral vascular disease and peripheral artery occlusive disease, is a type of cardiovascular disease, meaning it affects blood vessels and circulation. PAD can affect any artery within the body except those that supply the heart. It occurs when large arteries become obstructed, leading to a reduction in blood flow from the heart to the muscles in the limbs (most often the legs).¹ Most forms of PAD are caused by a gradual build-up of fatty material in the walls of the artery. This condition is called “atherosclerosis” and the fatty material is known as “atheroma”. In time, arteries may become so narrow that they cannot deliver enough oxygen-rich blood to the body’s extremities. The presence of atheroma can also cause a blood clot (thrombus) to form, blocking the artery completely. In severe cases or if the condition remains untreated, the blockage can cause gangrene, requiring amputation of the affected limb. Amputation is, however, relatively rare.

A SUMMARY OF PAD

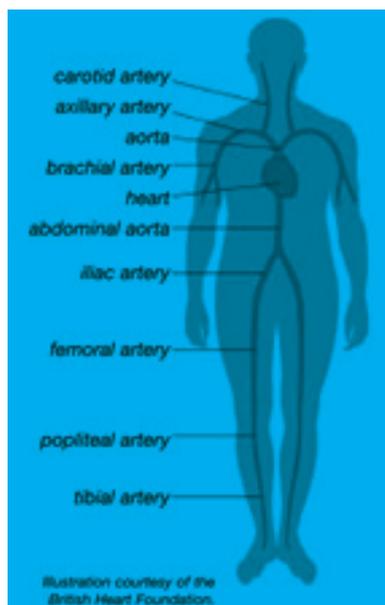
Smoking is the most important, preventable risk factor for PAD. Smokers have a significantly greater risk of developing PAD than people who have never smoked. Some types of peripheral arterial disease are almost exclusively found in smokers.

PAD is a common disorder but because it is not directly life-threatening, it has not received the same degree of attention or research as coronary heart disease. However, PAD may be a precursor to coronary heart disease since people with narrowed peripheral arteries are also more likely to have a narrowing of the coronary arteries.

PAD mostly occurs in the elderly. In the United Kingdom around 1 in 5 men and 1 in 8 women aged 50-75 years have PAD.

About half of all people with PAD have no obvious symptoms and the first indication of peripheral arterial disease may be a heart attack or stroke. Approximately 50% of all patients diagnosed with PAD will die within five years and about 70% within ten years, primarily due to a heart attack.

The most effective treatment for PAD is to stop smoking. This single measure reduces the risk of disease progression amongst patients with peripheral arterial disease and dramatically reduces the need for limb amputation and the risk of premature death.



WHAT ARE THE SYMPTOMS OF PAD?

Three quarters of all people with PAD are asymptomatic. Symptoms of PAD vary depending on what part of the body is affected. The most common symptom is intermittent claudication, which is experienced as pain or cramping in the lower leg and less commonly in the thighs or feet.^{2,3} Often this pain will come on after walking or other exercise and will disappear within a few minutes of stopping.

In most people with intermittent claudication, the symptoms remain stable but approximately 20% of people will develop increasingly severe symptoms leading to the development of critical limb ischaemia.⁴ Critical limb ischaemia is characterised by ulceration, tissue loss and/or gangrene, pain, and severely diminished circulation. Overall, 1-3% of people with critical ischaemia will eventually require limb amputation,^{5,6} whilst many more die within 5 years of presentation.⁷ The figure rises to 5% in those with diabetes.⁸

WHO IS AT RISK OF PAD?

Smokers and former smokers who are less than 10 years smoke-free, as well as those exposed to considerable amounts of secondhand smoke (SHS) are at significant risk of developing PAD. (See below for details.) Risk⁹ and prevalence increase with age, with a three-fold escalation in risk every ten years after a person's 40th birthday.¹⁰ Research shows that about 20% of people aged 60 or older have at least some degree of PAD.¹¹

A US study found that PAD was present in 32% of men and 26% of women with a mean age of 80 and 81 respectively.¹² The Framingham study, based on a sample of over 3,000 patients in the US, documented a two-fold male predominance (1.8% for women and 3.6% for men).^{13,14} However, the Edinburgh Artery Study failed to demonstrate any significant difference in PAD between men and women.¹⁵ This was confirmed by an international research team that collated data from 34 previous studies involving a total of 112,027 participants. The researchers established that rates of PAD increased with age but were similar among men and women in both high and low-middle income countries, especially as they aged.^{16,17} More recent research found that women participating in a five-year longitudinal study had a higher prevalence of PAD, compared to men. Neither higher C-reactive protein levels nor conventional cardiovascular disease (CVD) risk factors explained the excess prevalence of PAD in women.¹⁸ More research is needed to determine the exact risk levels of PAD of men and women and if or how the disease affects them differently.

HOW MANY PEOPLE ARE AFFECTED?

The international research team referred to above also reported that in 2010 there were about 202 million people globally living with PAD – about a 20% increase since 2000.¹⁹ Nearly 70% of these were in low-middle income countries, which included 54.8 million in Southeast Asia and 45.9 million in the Western Pacific Region.²⁰ PAD is now a global problem.

According to data from the Quality and Outcomes Framework (QOF), 446,000 people in the UK had PAD in 2013-14.²¹ PAD affects 4-12% of people aged 55-70 years and 15-20% of people aged over 70 years.²²

Research has found that 1 in 5 men and 1 in 8 women aged 50-75 years in the UK have PAD.²³ A more recent UK study found the rate of PAD in men and women to be similar,²⁴ perhaps because smoking rates among women are now similar to those among men or because women typically live longer than men since PAD becomes more common with increasing age.²⁵ By age 90, the lifetime risk for PAD in England is 2.6% for non-smokers and 8.9% for smokers.²⁶

ASSOCIATION BETWEEN SMOKING AND PAD

An association between smoking and PAD was first reported over 100 years ago.²⁷ It wasn't until 1949, however, that the first major longitudinal association between smoking and PAD was established in the US Framingham study.²⁸ Since that time, research has consistently revealed that smoking is the leading modifiable risk factor for PAD.^{29 30 31 32} In fact, smoking is considered a direct cause of PAD,³³ 50% of it being attributable to smoking.^{34 35}

The National Health and Nutrition Examination Survey (1999-2000) reported that smoking accounted for the majority of PAD diagnoses, followed by ethnicity, diabetes, poor kidney function, hypertension (raised blood pressure) and hyper-cholesterolaemia (high levels of blood cholesterol).^{36 37} PAD is also particularly common in patients with multiple cardiovascular risk factors and is associated with significant morbidity and mortality.³⁸

The Edinburgh Artery Study and others have found that current smokers are almost four times as likely to develop asymptomatic PAD as non-smokers.^{39 40 41} There is a mean odds ratio of 2.3 for development of symptomatic PAD or critical limb ischemia (CLI) among current smokers of both sexes.^{42 43}

In 2013, a group of researchers from Glasgow published data from over 50 studies on the association between PAD and smoking,⁴⁴ reporting that smoking more than doubled an individual's risk of developing PAD. The magnitude of this association was greater than that reported previously for coronary heart disease.^{45 46} Smokers have also been found to have a greater risk of developing symptomatic as opposed to asymptomatic PAD, in particular an increased risk of intermittent claudication. They also experience symptoms 10 years earlier than non-smokers.⁴⁷

For those diagnosed with PAD, continuing smoking is associated with poorer measures of exercise capacity during treadmill testing, including peak oxygen uptake and earlier onset of claudication pain during walking.^{48 49 50} This may be one reason why smokers with PAD report a lower quality of life than non-smokers with PAD.⁵¹

A large Chinese study found that the risk of PAD in former smokers was similar to that of current smokers who had quit within the past 10 years, but the risk was greatly reduced after 10 years or more.⁵²

A dose-dependent relationship between smoking and PAD has been reported with a greater cigarette consumption associated with increased risk.^{53 54 55 56 57 58} Duration of smoking is also a predictor of disease development and progression. A US study found that those who have smoked for less than 25 years have a three-fold increased risk of developing PAD compared to non-smokers, while those who have smoked for 25 years or more have a five-fold increased risk.⁵⁹

The risks of PAD are cumulative when additional risk factors are present, including raised cholesterol levels, raised blood pressure, age, sex, family history, diabetes, obesity and raised homocysteine levels.⁶⁰ (Homocysteine is an amino acid. Elevated plasma levels of homocysteine are associated with hardening or blocking of the arteries.) Another US study found that more than 95% of people with PAD had one or more cardiovascular disease risk factors.⁶¹ While those diagnosed with diabetes have a significantly increased risk of PAD compared to those without diabetes, this risk is increased by a further 50% if they use tobacco products.⁶²

HOW SMOKING CAUSES PAD

Perhaps the earliest injurious effects of smoking on the development of PAD are those which result in abnormal vasodilator responses of arteries. The inhalation of cigarette smoke results in the absorption of nicotine within seconds, with a consequent release of adrenaline and noradrenaline (neurotransmitters). These bind to receptors within the muscular wall of vessels to cause vasoconstriction (narrowing of the blood vessels from contraction of the muscular wall of the vessel). In non-smoking adults this effect is counterbalanced by the release of vasodilators (widening of the blood vessels from relaxation of the muscular wall of the vessel). However, in smokers the production of vasodilators is often impaired. In normal, healthy non-smoking adults brachial (large artery of the upper arm) and femoral (large artery in the thigh) arteries dilate by 11% and 4% respectively, while in young, apparently healthy smokers, these dilations are reduced to 4% and 0% respectively.⁶³

HOW SMOKING CAUSES PAD (CONTINUED)

Carbon monoxide, a poisonous gas produced from smoking, also results in damage by reducing oxygen supply. This happens when carbon monoxide in tobacco smoke attaches to haemoglobin (found in red blood cells) in place of oxygen and leads to elevated levels of carboxyhaemoglobin. Carbon monoxide also results in a thickening of the blood making it even harder for oxygen to reach tissues.⁶⁴ The net result is ulceration and, in extreme cases, gangrene in the limbs. When the blood's ability to carry oxygen around the body is reduced, the chance of a blood clot occurring is increased.⁶⁵ Formation of a blood clot can result in stroke or heart attack, both of which can be fatal.

Tobacco use also leads to atherosclerosis, the principal cause of PAD. This refers to the development of a plaque in the wall of an artery that leads to narrowing of the artery and reduction in blood flow to the limbs. Smoking-related atherosclerosis is caused by chemicals in tobacco smoke directly damaging endothelial cells lining the walls of blood vessels. This enhances the transfer of low-density lipoprotein cholesterol (bad cholesterol) across the arterial wall and results in the build-up of fatty plaques.⁶⁶ At the same time, cigarette smoking lowers levels of the protective high-density lipoprotein cholesterol (good cholesterol).⁶⁷

SPECIFIC TYPES OF PAD

BUERGER'S DISEASE

Buerger's disease, also called thromboangiitis obliterans, is a relatively rare form of PAD that most commonly affects the small- and medium-sized blood vessels (arteries and veins) of the arms and legs.⁶⁸ The prevalence of the disease varies from as low as 0.5% to 5.6% in Western Europe to as high as 45% to 63% in India, and 16% to 66% in Korea and Japan,⁶⁹ making it far more prevalent in the Middle East and Far East.⁷⁰ The disease typically occurs in young male smokers, aged 20 to 40, although it can also occur in women.^{71 72}

Buerger's disease is characterised by the swelling of blood vessels, which prevents blood flow and causes clots to form. This can lead to pain, tissue damage and even gangrene. In some cases, amputation may be required.⁷³ In 2004, Cooper found that the risk of amputation during 15.6 years of follow-up in patients with Buerger's disease was 25% at five years, 38% at 10 years and 46% at 20 years.^{74 75}

There is an extremely strong association between the use of tobacco and Buerger's disease,⁷⁶ with just 5% of patients being non-smokers.⁷⁷ There is also some evidence to suggest that users of smokeless tobacco are also at risk,^{78 79 80} as well as those exposed to significant amounts of secondhand smoke (SHS).⁸¹ Mechanisms by which this occurs include tobacco's effect on the triggering of an immune response in susceptible persons or unmasking a clotting defect; either of which incites an inflammatory reaction of the vessel wall.

Marijuana use has also been considered a risk factor for developing Buerger's disease.⁸³

Nearly two thirds of patients with Buerger's disease have severe periodontal disease and chronic periodontal infection may be an additional risk factor for developing the disease.⁸⁴

The only proven treatment to prevent progression of the disease and avoid amputation is the complete cessation of smoking or other use of tobacco.^{85 86 87} Smoking cessation leads to dramatic improvements of the symptoms, but relapse quickly reactivates the disease.⁸⁸ In a Japanese study, 19% of patients diagnosed with thromboangiitis obliterans who continued to smoke required amputation, while none of those who stopped underwent amputation.⁸⁹ In a smaller study of 27 Spanish cigarette smokers, all who achieved abstinence had improvement in their disease and none underwent amputation, compared to 50% of those who resumed smoking and later required amputation.⁹⁰

VISCERAL ARTERIAL OCCLUSIVE DISEASE

Visceral arterial occlusive disease, also called mesenteric occlusive disease, occurs when the mesenteric arteries become occluded (blocked) and the blood supply is limited to the intestines, spleen and liver. The mesenteric arteries are the major arteries that supply the stomach, intestines, liver, spleen, pancreas and gallbladder. Symptoms start gradually, usually with cramp-like abdominal pain particularly after a meal, followed by diarrhoea, constipation and vomiting. This leads to subsequent weight loss.

Smoking has been shown to be a risk factor for mesenteric occlusive disease in a number of studies. For example, one study found that smoking was nearly twice as common in patients with non-malignant hypertension associated with renal artery stenosis (narrowing of the kidney arteries) as in those patients with hypertension of comparable severity without renal artery disease.⁹¹ Another study reported that recurrent symptoms of chronic mesenteric ischaemia occurred predominantly in female patients who were heavy smokers.⁹²

ABDOMINAL AORTIC ANEURYSM

Abdominal aortic aneurysm (AAA) is a widening or dilation of the aorta in the abdomen. The aorta carries the blood pumped out of the heart to the rest of the body. It is usually around 2-3 cm in diameter. A weak spot in the aorta can cause it to bulge out. This is called an aneurysm. Abdominal aortic aneurysm is common in the elderly but often remains undiagnosed until a rupture occurs, which carries a fatality rate of over 90%.⁹³ Of those who undergo emergency repair, mortality is over 40%.⁹⁴

AAA is uncommon in people under 50, but 12.5% of men and 5.2% of women in the US aged 74 to 84 years have it.⁹⁵

Smoking is the risk factor most strongly associated with abdominal aortic aneurysms,^{96 97 98} followed by age, high blood pressure and high cholesterol levels. The risk for developing AAA is even higher among smokers than it is for either coronary artery disease or stroke.⁹⁹

Since screening has been shown to improve AAA-related mortality in this population, men aged 65-75 with a history of smoking are encouraged to undergo one-time ultrasound screening for AAA.¹⁰⁰ A free national screening programme is available in the UK to men in the year they turn 65.^{101 102} Women are not routinely included because they are six times less likely to develop an AAA.¹⁰³ However, at this time in the UK, women 65 and older and men and women under 65 may still request a scan if they haven't been offered one.¹⁰⁴

As discussed, smokers in general are at higher risk of developing AAA, but heavy smokers are at a much greater risk. Research has found that risk increases as a function of the amount and duration of smoking,¹⁰⁵ and prognosis is negatively affected by continued smoking. Although AAA is much less common in women, outcomes appear to be worse than in men with AAA.^{106 107}

A study of 1,412 male patients from 1965 to 1970 established that heavy smokers have as much as an eight-fold increase in the incidence of abdominal aortic aneurysm.¹⁰⁸ This was confirmed in a large study conducted in Norway. Ultrasound was used to assess presence of AAA in 1994, with a repeat test 7-8 years later. Smoking increased the risk of AAA over ten-fold compared to never smokers, while hypertension and hypercholesterolaemia increased the odds of AAA only two-fold.¹⁰⁹

In a small study, risk of rupture was more common among current smokers and those with hypertension.¹¹⁰ Smoking has also been found to increase the rate of growth of abdominal aneurysms¹¹¹ to up to 0.4 mm per year^{112 113 114} and to impair recovery and success of treatment.¹¹⁵ Another study found that smoking was considered to be responsible for 75% of the excess prevalence of AAAs ≥ 4 cm.¹¹⁶

Theories to explain the influence of smoking on AAA include disruption in collagen synthesis and increased level of oxidative stress.^{117 118} Collagen is a group of naturally occurring proteins found in connective tissues such as tendons, ligaments and the skin, while oxidative stress refers to an imbalance between the production of reactive oxygen and the ability to detoxify the reactive intermediates or easily repair the resulting damage. Compared to non-smokers with AAA, smokers with AAA are also more likely to present with respiratory-transmitted viruses, which accelerate AAA development.¹¹⁹

ABDOMINAL AORTIC ANEURYSM (CONTINUED)

Stopping smoking may therefore slow down the growth of the aneurysm and reduce the risk of rupture and premature death. Support for this hypothesis comes from a study conducted in the UK in 1999 on around 500 participants. Ex-smokers were three times more likely to have an AAA than non-smokers, but less likely to have an AAA than continuing smokers. Duration of smoking was found to be significantly associated with risk. Each year of smoking increased the risk by 4%.¹²⁰ The largest study to date, conducted in the US on 3.1 million patients, also reported that smoking cessation was associated with a lower risk of AAA. However, data was retrospective (requiring individuals to recall their past smoking behaviour), which means that some patients may have forgotten or misreported their behaviour.

In another study, smoking was found to impact on AAA surgery outcome. Mortality and complications of 3,270 patients who underwent surgery for AAA in Europe between 1994 and 2001 were assessed. This research showed that mortality did not differ between smokers and non-smokers, and smokers had a higher number of additional complications.¹²¹ Other research, however, has found that smoking history was associated with a worse long-term survival hazard ratio of 1.27.¹²²

RISK OF CHD OR STROKE

People with PAD are also likely to have narrowed arteries in other parts of the body. If there is a narrowing in the coronary arteries (which supply blood to the heart muscle), this can cause chest pain (angina) or a heart attack. If the arteries to the neck are affected, it can interfere with the flow of blood to the brain and may cause a stroke.¹²³ PAD can therefore be a precursor to other forms of coronary heart disease (CHD).

Studies show that around a third of patients with intermittent claudication have evidence of cardiovascular disease and that PAD carries at least a 50% risk of death within five years, primarily due to a heart attack.¹²⁴ In a study of over 6,880 patients, those with PAD at five years follow-up were found to be twice as likely to have suffered an ischaemic stroke, haemorrhagic stroke and fatal stroke as those without PAD at baseline.¹²⁵ Research shows that 60-80% of those with PAD have coronary artery disease in at least one coronary artery.¹²⁶ About 90% of people with severe PAD have CHD.¹²⁷ People with PAD are also at risk of developing coronary artery disease and cerebrovascular disease. People with PAD have a 6-7 times higher-than-average risk of having a heart attack or stroke.¹²⁸

It follows that, as the population now lives longer with chronic diseases, it is estimated that the incidence of PAD will increase in future, likely increasing heart attacks, stroke and related death.¹²⁹

SECONDHAND SMOKE AND PAD

There is now considerable evidence to show that exposure to secondhand smoke (SHS) increases the risk of coronary heart disease (CHD) in non-smokers^{130 131} and the risk of a heart attack by 30%.¹³² The mechanisms by which these occur suggest that secondhand smoke exposure could also increase the risk of PAD.¹³³ For example, arterial endothelial dysfunction has been reported to be associated with SHS exposure¹³⁴ and non-smokers exposed to tobacco smoke have been shown to have greater levels of atherosclerosis, compared to people not exposed.¹³⁵ Other research suggests that exposure to SHS may exert an adverse effect on platelet activation in the peripheral arteries.¹³⁶

Despite the hypothesis of an association between SHS exposure and PAD as a consequence of the research on CHD, results regarding an association have been mixed.¹³⁷ The handful of studies that have been conducted thus far either report a positive association between SHS exposure and risk of diagnosis of PAD or have failed to find any evidence of a relationship. Nevertheless, US clinical practice guidelines recommend that all people with PAD avoid SHS at work, at home and in public places.¹³⁸

SECONDHAND SMOKE AND PAD (CONTINUED)

A study of 1,209 Chinese women who had never smoked found that those exposed to SHS in the home or at work were 67% more likely to develop PAD than those without regular exposure. The more time spent in a smoky environment, the greater the risk of PAD, coronary heart disease and stroke.^{139 140 141} The findings of the Chinese research were confirmed in a UK study, where SHS exposure was shown to be an independent risk factor for PAD: 3% of those with PAD reported being exposed to SHS for 40 or more hours per week, compared to less than 1% of those not diagnosed with PAD.¹⁴² In contrast, a US study of 7,550 individuals in the National Health and Nutrition Examination Survey (NHANES) failed to establish an association between SHS exposure and risk of developing PAD. This was supported by Agarwal in 2009, who used data from a nationally representative sample of the US population.¹⁴³

It has been suggested that higher doses of chemicals from tobacco are required to damage arteries in the legs compared to those in the heart and brain.¹⁴⁴ This is supported by the threshold effect, where PAD risk is increased with the level of tobacco exposure. Another explanation is poor self-report of SHS exposure. In Agarwal's study, substantial overlap in non-smokers who reported and did not report SHS exposure was found in an objective biological measure of SHS exposure.

THIRDHAND SMOKE AND PAD

Recent research shows that polycyclic aromatic hydrocarbons (PAHs) found in thirdhand smoke (the residue of nicotine and other chemicals left on surfaces by tobacco smoke) may increase the risk of PAD, independent of smoking.¹⁴⁵ People are exposed to these chemicals by touching contaminated surfaces or by breathing in related off-gassing.

PAD TREATMENT

It is important to note that PAD is both under-diagnosed and under-treated.

There are two main treatments used in the management of PAD. The first involves making lifestyle changes to improve symptoms and reduce the progression of narrowing within the artery, while the second involves taking medication to address the underlying causes, such as cholesterol lowering tablets to keep cholesterol levels within desirable limits. Surgery may also be required in some cases.

The type of treatment given to patients will depend on the extent and severity of the conditions. When the PAD symptoms only involve intermittent claudication, individuals may be able to slow the progression of the disease simply by stopping smoking, modifying their diet and/or taking up exercise. All patients with resting pain, ulceration, or gangrene should be referred to a specialist for assessment.¹⁴⁷

Research has found that symptoms of PAD improve following smoking cessation and that exercise helps reduce the severity and frequency of symptoms. For example, studies have shown that by stopping smoking, 8 out of 10 people with PAD can increase their walking distance by two- or three-fold.¹⁴⁸ The National Institute for Health and Care Excellence (NICE) recommends smoking cessation and supervised exercise as two of the first steps in managing PAD.¹⁴⁹ The preferred exercise is walking. It is normally recommended that patients walk as far and as long as they can and stop to rest when required. They should keep using this start-stop method until they have spent 30-60 minutes walking per day.

Different medications can be used to treat the underlying causes of PAD while reducing the risk of developing another CVD. Statins are used to treat high levels of bad cholesterol, while anti-hypertensives can treat high blood pressure. Antiplatelet medication is also commonly prescribed in order to reduce the risk of a blood clot.¹⁵⁰ This medication works by diminishing the ability of tiny blood cells to stick together. Finally, a pain relief drug is used in the treatment of intermittent claudication to improve blood flow and reduce pain. Patients taking medication for PAD are encouraged to stop smoking, as tobacco use may undermine its effectiveness.¹⁵¹

FURTHER INFORMATION AND RESOURCES

Vascular Society of Great Britain and Ireland

The Vascular Society of Great Britain and Ireland funds research into vascular disease, provides patient information and aims to raise awareness of vascular disease amongst the general public.

[Home Page](#)

[Peripheral Arterial Disease](#)

[Lower limb peripheral arterial disease](#)

National Institute for Health and Care Excellence

NICE has a number of resources on peripheral arterial disease, including the most recent (2012) guidance, as well as a guidance on smoking cessation.

[Home Page](#)

[PAD Search Page](#)

[Lower limb peripheral arterial disease: Diagnosis and management](#)

[Stop smoking services](#)

The Circulation Foundation

The Circulation Foundation publishes a number of free patient information leaflets to help identify and treat vascular illness. It also funds research into the prevention and causes of vascular disease.

[Home Page](#)

[Peripheral Arterial Disease](#)

PAD TREATMENT (CONTINUED)

In more severe cases of PAD, there are two types of invasive treatments: angioplasty and bypass surgery. Arterial bypass surgery involves diverting blood that is not able to flow down a blocked artery through an artificial vessel to reach the tissues that need it. Some bypass surgeries fail within a year, resulting in tissue death. At this point, amputation is urgently needed. The risk of failure can be reduced by stopping smoking.

Angioplasties are a more common form of treatment. This procedure flattens fatty deposits against the walls of the blood vessel by using a tiny balloon at the end of a catheter, which is usually inserted into the artery at the patient's groin. When the end of the catheter reaches the blockage, the balloon is inflated to create space inside the blood vessel and sometimes a stent is inserted at this point, to help keep the artery open. The balloon is then deflated and removed.¹⁵²

THE BENEFITS OF STOPPING SMOKING

While there are pharmacological therapies and surgical options available for the treatment of PAD, stopping smoking is an important means of stabilising or improving the condition. In 2012, the National Institute for Health and Care Excellence published its updated guidance on the treatment and management of PAD. The guidance recognises smoking as the most important risk factor for PAD and recommends smoking cessation with the aid of medicinal and behavioural support.¹⁵⁶

There is substantial evidence that stopping smoking reduces the risk of disease progression amongst patients with PAD and dramatically reduces the need for limb amputation and the risk of premature death.¹⁵⁷ Conen and colleagues in 2011¹⁵⁸ published a study in the US on 39,825 women with no known cardiovascular disease whom they had followed for over 13 years. They reported a significant decrease in risk of PAD among former compared to current smokers, but nonetheless, the risk remained significantly increased among former smokers compared with never smokers. This finding has been confirmed by other researchers. In a smaller study of 245 women with PAD¹⁵⁹ the risk of PAD dropped dramatically after stopping smoking. In ex-smokers who had not smoked for 5 years or more the risk was near normal. Patients who had not smoked for between 1-5 years had a two-fold increased risk. By contrast, patients who continued to smoke up to 20 cigarettes a day had a 12-fold increased risk. However, a large Chinese study found that the risks of former smokers didn't equal those of non-smokers until they had been smoke-free for 10 years.¹⁶⁰

In terms of mortality, studies suggest that smoking cessation decreases the risk of death from PAD-related complications, but that the effect is often delayed. In one study of over 2,500 patients with PAD, no association between stopping smoking and reduction in risk of death was found within the first 14 months following cessation;¹⁶¹ while other studies point to a reduction in mortality of up to 50% over the longer term.^{162 163} Approximately 50% of all patients diagnosed with PAD will die within five years and about 70% within ten years, primarily due to a heart attack.¹⁶⁴

FURTHER INFORMATION AND RESOURCES

British Heart Foundation

The BHF is a useful resource for all facets of vascular and coronary health.

[Home Page](#)

[PAD Search Page](#)

[Focus on: Peripheral arterial disease](#)

[Cardiovascular Disease Statistics 2015](#)

[European Cardiovascular Disease](#)

[Statistics 2017](#)

National Health Service

The NHS provides information products for the public and health professionals.

[Peripheral arterial disease](#)

[Peripheral arterial disease](#)

US Surgeon General reports and related information

[The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014](#)

[How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease](#)

[The Health Consequences of Involuntary Exposure to Tobacco Smoke](#)

[The Health Benefits of Smoking Cessation: A Report of the Surgeon General](#)

[The Health Consequences of Smoking: Cardiovascular Disease](#)

[Peripheral Arterial Disease \(PAD\) Fact Sheet](#)

[Smoking and Cardiovascular Disease](#)

THE BENEFITS OF STOPPING SMOKING (CONTINUED)

Research is more conclusive regarding symptom severity. Smoking cessation leads to improvements in leg symptoms, lowers the amputation risk and reduces the cardiovascular event rate.^{165 166} Juergens and colleagues reported in a small study that approximately 10% of those who continued to smoke eventually required amputation, but no amputations were necessary in patients who successfully stopped smoking.¹⁶⁷

Stopping smoking also affects the long-term success rate of reconstructive arterial surgery. For example, there is a three-fold increased likelihood of failure of a bypass in the femoral artery in those who continue to smoke more than five cigarettes a day, compared to those who do not smoke or smoke fewer than five cigarettes per day.¹⁶⁸ Studies have shown that the patency rate (the rate at which the artery remains unobstructed) is significantly lower among smokers one year after surgery compared to non-smokers.¹⁶⁹

A number of studies have assessed the effectiveness of smoking cessation treatment on PAD symptoms. For example, in one study 390 patients with PAD, who were either ineligible or unfit to undergo operative treatment, were given advice including cessation of smoking, walking exercise, a low cholesterol diet, and vitamin E therapy. Of 277 patients who smoked, 164 stopped smoking following treatment. Eighty-five per cent of patients who stopped smoking showed improvement in symptoms of PAD compared with only 20 per cent among those who continued to smoke. Interestingly, the degree of improvement was greater among the ex-smokers than those who had never smoked, demonstrating over four decades ago that smoking is a key modifiable risk factor for PAD.¹⁷⁰

As a whole, this research demonstrates that stopping smoking is essential for people with PAD. Those who do so may avoid surgery while those who continue to smoke may lose a limb whether or not they have surgical treatment. Unfortunately, some studies show that people with PAD do not associate their symptoms with their own behaviour, such as smoking, and may have the perception that managing the disease is beyond their control.¹⁷¹

Smokers and former smokers should be asked about the status of their tobacco use at every physician visit,^{172 173} given the difficulty in quitting and the high rate of relapse.^{174 175} Smokers should be asked to quit in order to help prevent PAD.¹⁷⁶ All patients with PAD (or CVD in general) should also be strongly encouraged to quit smoking immediately and permanently.^{177 178} Nicotine replacement therapy (NRT) and/or bupropion or varenicline can help patients quit smoking, especially

those with a high level of nicotine dependence.¹⁷⁹ All three of the medications listed above are safe to use in patients with cardiovascular disease^{180 181} and should be recommended barring any contraindications.¹⁸²

Although some vascular surgeons may feel that they don't have time to undertake smoking cessation counselling, brief interventions are feasible and can be effective.¹⁸³ One study has shown that brief counselling by vascular surgeons has the potential to impact the desire of patients with PAD to quit. When surveyed three months after a brief intervention, patients in the intervention group showed larger declines in nicotine dependence.¹⁸⁴ It is important to note that more intensive interventions are indeed more effective in supporting patients' quit attempts.¹⁸⁵

SMOKING PREVENTION

Although smoking cessation is crucial in the treatment and prevention of PAD in the shorter term, non-smokers of all ages, but especially youth and young adults, should be encouraged by their physicians never to start smoking.¹⁸⁶ This is particularly important to prevent PAD over the longer term since it often goes undiagnosed.¹⁸⁷

ASH POLICY RECOMMENDATIONS

Despite PAD being a serious consequence of smoking it is poorly understood by the public. Many people simply do not realise that smoking can cause such grave damage to their limbs. Because PAD is such a major threat to public health, and a significant drain on the National Health Service (NHS), ASH recommends the following policy measures, which are supported by experts in the field:

- The health consequences of PAD (e.g. gangrene and amputation) should be included in the range of pictorial health warnings to be featured on cigarette packs. Countries such as Brazil and Australia include these in their range of pictorial health warnings.
- The risk of PAD to smokers should be included in Government anti-smoking campaigns to increase awareness of this serious condition.
- Health practitioners should routinely warn patients who smoke of the risks of peripheral arterial disease and implement the NICE guidance on the diagnosis and management of PAD.¹⁸⁸
- Smokers diagnosed with PAD should be encouraged to quit and offered support to reduce the risk of developing other coronary artery diseases, stroke or a heart attack, and to help arrest the symptoms that can reduce quality of life among people with PAD
- Currently the Abdominal Aortic Aneurysm Screening Service is only routinely offered to men over 65 but in light of new evidence suggesting the gender differences in risk of PAD are not as great as once observed, research should be conducted to evaluate the need to extend screening programmes to women who smoke or have ever smoked.

References:

1. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. – Atlanta, GA. : U.S. 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. <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html#>
2. National Clinical Guideline Centre. Lower limb peripheral arterial disease: Diagnosis and management. NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012. <https://www.nice.org.uk/guidance/cg147/evidence/lower-limb-peripheral-arterial-disease-full-guideline-186865021>
3. Peach G, Griffin M, Jones KG, et al; [Diagnosis and management of peripheral arterial disease](#). BMJ. 2012 Aug 14 345:e5208.
4. National Clinical Guideline Centre. Lower limb peripheral arterial disease: Diagnosis and management. NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012. <https://www.nice.org.uk/guidance/cg147/evidence/lower-limb-peripheral-arterial-disease-full-guideline-186865021>
5. Kannel WB, Skinner JJ, Jr., Schwartz MJ, Shurtleff D. [Intermittent claudication. Incidence in the Framingham Study](#). Circulation. 1970; 41(5):875-883
6. Peach G, Griffin M, Jones KG, et al; [Diagnosis and management of peripheral arterial disease](#). BMJ. 2012 Aug 14 345:e5208.
7. Davis, M. Critical limb ischaemia, ulcers and gangrene. The Royal Free Hospital Vascular Unit. 2005. 17-3-2005.
8. Peripheral Arterial Disease; NICE CKS, April 2014.
9. National Clinical Guideline Centre. Lower limb peripheral arterial disease: Diagnosis and management. NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012. <https://www.nice.org.uk/guidance/cg147/evidence/lower-limb-peripheral-arterial-disease-full-guideline-186865021>
10. Hiatt WR. Pharmacologic therapy for peripheral arterial disease and claudication. J Vasc Surg. 2002;36(6):1283–91. [http://www.jvascsurg.org/article/S0741-5214\(02\)00330-0/pdf](http://www.jvascsurg.org/article/S0741-5214(02)00330-0/pdf)
11. Fowkes FG, Housley E, Cawood EH, et al. [Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population](#). International Journal of Epidemiology. 1991; 20(2):384-392
12. Aronow WS, Ahn C, Gutstein H. [Prevalence and incidence of cardiovascular disease in 1160 older men and 2464 older women in a long-term health care facility](#). J Gerontol Med Sci 2002; 57A:M45-M46.
13. Murabito JM, Evans JC, Nieto K, et al. [Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study](#). Am Heart J 2002; 146(6): 961-5.
14. Patient. Peripheral arterial disease. September 21, 2015. <http://patient.info/health/peripheral-arterial-disease-leaflet>
15. Leng GC, Lee AJ, Fowkes FG, et al. [Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population](#). In J Epidemiol. 1996; 25(6):1172–81.
16. Fowkes FGR, Rudan D, Rudan I, et al. [Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis](#). Lancet. 2013 Oct 19;382(9901):1329-40.
17. Patient. Peripheral arterial disease. September 21, 2015. <http://patient.info/health/peripheral-arterial-disease-leaflet>
18. Hiramoto JS, Katz R, Weisman S, Conte M. [Gender-Specific Risk Factors for Peripheral Artery Disease in a Voluntary Screening Population](#). Journal of the American Heart Association. 2014 Mar 13;3(2):e000651.
19. Fowkes FGR, Rudan D, Rudan I, et al. [Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis](#). Lancet. 2013 Oct 19;382(9901):1329-40.
20. Fowkes FGR, Rudan D, Rudan I, et al. [Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis](#). Lancet. 2013 Oct 19;382(9901):1329-40.
21. British Heart Foundation. Cardiovascular Disease Statistics 2015. 08/12/2015. <https://www.bhf.org.uk/publications/statistics/cvd-stats-2015>
22. Peach G, Griffin M, Jones KG, et al; [Diagnosis and management of peripheral arterial disease](#). BMJ. 2012 Aug 14 345:e5208.
23. Patient. Peripheral arterial disease. September 21, 2015. <http://patient.info/health/peripheral-arterial-disease-leaflet>
24. Howard DP, Banerjee A, Fairhead JF, et al. Population-Based Study of Incidence, Risk Factors, Outcome, and Prognosis of Ischemic Peripheral Arterial Events: Implications for Prevention. Circulation. 2015 Nov 10;132(19):1805-15. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4633967/pdf/cir-132-1805.pdf>
25. Patient. Peripheral arterial disease. September 21, 2015. <http://patient.info/health/peripheral-arterial-disease-leaflet>
26. Pujades-Rodriguez M, George J, Shah AD, et al. [Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1937360 people in England: lifetime risks and implications for risk prediction](#). Int J Epidemiol. 2015 Feb;44(1):129-41.
27. Erb, W. Klinische Beiträge zur Pathologie des intermittierenden Hinkens. Munch Med Wochenschr 1911;2:2487.
28. United States Public Health Service. Office of the Surgeon General and Office on Smoking and Health. The health consequences of smoking: Cardiovascular disease. A report of the Surgeon General. Rockville, US PHS, 1983. <https://profiles.nlm.nih.gov/NN/B/B/T/D/>
29. National Clinical Guideline Centre. Lower limb peripheral arterial disease: Diagnosis and management. NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012. <https://www.nice.org.uk/guidance/cg147/evidence/lower-limb-peripheral-arterial-disease-full-guideline-186865021>
30. Lu JT, Creager MA. The relationship of cigarette smoking to peripheral arterial disease. Rev Cardiovasc Med. 2004 Fall;5(4):189-93.
31. Shamoun FE, Fankhauser GT, Mookadam M. Vascular medicine: aortic and peripheral arterial disease. Prim Care. 2013 Mar;40(1):169-77.
32. Teodorescu VJ, Vavra AK, Kibbe MR. [Peripheral arterial disease in women](#). J Vasc Surg. 2013 Apr;57(4 Suppl):18S-26S.
33. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. – Atlanta, GA. : U.S. 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. <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html#>

References (continued):

34. Lu L, Mackay DF, Pell JP. [Meta-analysis of the association between cigarette smoking and peripheral arterial disease](#). *Heart*. 2014 Mar;100(5):414-23.
35. Willigendael EM, Teijink JA, Bartelink ML, et al. [Influence of smoking on incidence and prevalence of peripheral arterial disease](#). *J Vasc Surg* 2004;40:1158-65.
36. Selvin E, Erlinger TP. [Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000](#). *Circulation* 2004;110(6):738-43.
37. European Society of Cardiology. [Diagnosis and Treatment of Peripheral Artery Diseases](#). 2011.
38. Alahdab F, Wang AT, Elraiyah TA, et al. [A systematic review for the screening for peripheral arterial disease in asymptomatic patients](#). *J Vasc Surg*. 2015 Mar;61(3 Suppl):42S-53S.
39. Fowkes FG, Housley E, Cawood EH, et al. [Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population](#). *International Journal of Epidemiology*. 1991; 20(2):384-392
40. Das JR, Eberhardt RT. [Contemporary risk assessment and cardiovascular outcomes in peripheral arterial disease](#). *Cardiovasc Hematol Disord Drug Targets*. 2013 Dec;13(3):185-96.
41. Teodorescu VJ, Vavra AK, Kibbe MR. [Peripheral arterial disease in women](#). *J Vasc Surg*. 2013 Apr;57(4 Suppl):18S-26S.
42. Willigendael EM, Teijink JA, Bartelink ML, et al. [Influence of smoking on incidence and prevalence of peripheral arterial disease](#). *J Vasc Surg* 2004;40:1158-65.
42. Jensen SA, Vatten LJ, Myhre HO: [The prevalence of chronic critical lower limb ischaemia in a population of 20,000 subjects 40-69 years of age](#). *Eur. J. Vasc. Endovasc. Surg.* 32(1), 60-65 (2006).
44. Lu L, Mackay DF, Pell JP. [Meta-analysis of the association between cigarette smoking and peripheral arterial disease](#). *Heart*. 2014 Mar;100(5):414-23.
45. Huxley RR, Yatsuya H, Lutsey PL, et al. [Impact of age at smoking initiation, dosage, and time since quitting on cardiovascular disease in African Americans and Whites](#). *Am J Epidemiol* 2012;175:816-26.
46. Lu L, Mackay DF, Pell JP. [Meta-analysis of the association between cigarette smoking and peripheral arterial disease](#). *Heart*. 2014 Mar;100(5):414-23.
47. Schmieder FA, Comerota AJ. [Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies](#). *Amer J Cardiol*. 2001 Jun 28;87(12A):3D-13D
48. Afaq A, Montgomery PS, Scott KJ, et al. [The effect of current cigarette smoking on calf muscle hemoglobin oxygen saturation in patients with intermittent claudication](#). *Vasc Med*. 2007 Aug;12(3):167-73.
49. Gardner AW. [The effect of cigarette smoking on exercise capacity in patients with intermittent claudication](#). *Vasc Med*. 1996;1(3):181-6
50. Katznel LI, Sorkin JD, Powell CC, Gardner AW. [Comorbidities and exercise capacity in older patients with intermittent claudication](#). *Vasc Med*. 2001;6(3):157-62
51. Fritischi C, Collins EG, O'Connell S, et al. [The effect of smoking status on walking ability and health-related quality of life in patients with peripheral arterial disease](#). *J Cardiovasc Nurs*. 2013 Jul-Aug;28(4):380-6.
52. He Y, Jiang Y, Wang J, et al. [Prevalence of peripheral arterial disease and its association with smoking in a population-based study in Beijing, China](#). *J Vasc Surg*. 2006 Aug; 44(2):333-8.
53. Willigendael EM, Teijink JA, Bartelink ML, et al. [Influence of smoking on incidence and prevalence of peripheral arterial disease](#). *J Vasc Surg*. 2004 Dec;40(6):1158-65.
54. Vavra AK, Kibbe MR. [Women and peripheral arterial disease](#). *Womens Health (Lond)*. 2009 Nov;5(6):669-83.
55. Fowkes FG, Housley E, Riemersma RA, et al. [Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study](#). *Am J Epidemiol* 1992;135:331-40.
56. Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, et al. [Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication](#). *J Vasc Surg*. 2015 Mar;61(3 Suppl):2S-41S.
57. Norgren L, Hiatt WR, Dormandy JA, et al. [Inter-Society Consensus for the Management of Peripheral Arterial Disease \(TASC II\)](#). *Eur J Vasc Endovasc Surg*. 2007;33 Suppl 1:S1-75.
58. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. – Atlanta, GA. : U.S. 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. <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html#>
59. Leng GC, Lee AJ, Fowkes FGR. [The relationship between cigarette smoking cardiovascular risk factors in peripheral arterial disease compared with ischaemic heart disease. The Edinburgh Artery Study](#). *Eur Heart J*. 1995 Nov;16(11):1542-8.
60. Ball K. The role of cigarette smoking in vascular disease. In Greenhalgh RM, ed. *Smoking and arterial disease*. pp 9-16. London: Pitman Medical, 1981.
61. Selvin E, Erlinger TP. [Prevalence of and risk factors for peripheral arterial disease in the United States. Results from the National Health and Nutrition Examination Survey, 1999-2000](#). *Circulation*. 2004 Aug 10;110(6):738-43.
62. United States Public Health Service. Office of the Surgeon General and Office on Smoking and Health. The health consequences of smoking: Cardiovascular disease. A report of the Surgeon General. Rockville, US PHS, 1983. <https://profiles.nlm.nih.gov/NN/B/B/T/D/>
63. Davies M, Bland J, Haugartner J, et al. [Factors influencing the presence or absence of acute coronary artery thrombi in sudden ischaemic death](#). *Eur Heart J*. 1989 Mar;10(3):203-8.
64. Shimada S, Hasegawa K, Wada H, et al. [High blood viscosity is closely associated with cigarette smoking and markedly reduced by smoking cessation](#). *Circulation Journal*. 2011; 75(1):185-9.

References (continued):

65. Krupski WC. [The peripheral vascular consequences of smoking](#). Ann Vasc Surg. 1991 May;5(3):291-304.
66. Penn A, Chen LC, Snyder CA. [Inhalation of steady-state sidestream smoke from one cigarette promotes atherosclerotic plaque development](#). Circulation 1994 Sep;90(3):1363-7.
67. Rabkin SW. [Effect of cigarette smoking cessation on risk factors for coronary atherosclerosis: a control clinical trial](#). Atherosclerosis. 84 Nov;53(2):173-84.
68. Del Conde I, Peña C. [Buerger disease \(thromboangiitis obliterans\)](#). Tech Vasc Interv Radiol. 2014 Dec;17(4):234-40.
69. Cacione DG, Macedo CR, Baptista-Silva JC. [Pharmacological treatment for Buerger's disease](#). Cochrane Database Syst Rev. 2016 Mar 11;3:CD011033.
70. Piazza G, Creager MA. [Thromboangiitis obliterans](#). Circulation. 2010 Apr 27;121(16):1858-61.
71. Piazza G, Creager MA. [Thromboangiitis obliterans](#). Circulation. 2010 Apr 27;121(16):1858-61.
72. Dargon PT, Landry GJ. [Buerger's disease](#). Ann Vasc Surg. 2012 Aug;26(6):871-80.
73. Lockwood SJ, Bresler SC, Granter SR. [Politics, culture, and the legitimacy of disease: the case of Buerger's disease](#). Clin Rheumatol. 2016 Sep;35(9):2145-9.
74. Cooper LT, Tse TS, Mikhail MA, et al. [Long-term survival and amputation risk in thromboangiitis obliterans \(Buerger's disease\)](#). J Am Coll Cardiol. 2004 Dec 21;44(12):2410-1.
75. Cacione DG, Macedo CR, Baptista-Silva JC. [Pharmacological treatment for Buerger's disease](#). Cochrane Database Syst Rev. 2016 Mar 11;3:CD011033.
76. Klein-Weigel P, Volz TS, Zange L, Richter J. [Buerger's disease: providing integrated care](#). J Multidiscip Healthc. 2016 Oct 12;9:511-518. eCollection 2016.
77. Olin, J. [Thromboangiitis obliterans \(Buerger's disease\)](#). N Eng J Med. 2000 Sep 21;343(12):864-9.
78. O'Dell JR, Linder J, Markin RS, Moore GF. [Thromboangiitis obliterans \(Buerger's disease\) and smokeless tobacco](#). Arthritis Rheum. 1987 Sep;30(9):1054-6.
79. Lawrence PF, Lund OI, Jimenez JC, Muttalib R. [Substitution of smokeless tobacco for cigarettes in Buerger's disease does not prevent limb loss](#). J Vasc Surg. 2008 Jul;48(1):210-2.
80. Piazza G, Creager MA. [Thromboangiitis obliterans](#). Circulation. 2010 Apr 27;121(16):1858-61.
81. Klein-Weigel P, Volz TS, Zange L, Richter J. [Buerger's disease: providing integrated care](#). J Multidiscip Healthc. 2016 Oct 12;9:511-518. eCollection 2016.
82. Tanaka K. [Pathology and pathogenesis of Buerger's disease](#). Int J Cardiol 1998; 66: 237-42.
83. Piazza G, Creager MA. [Thromboangiitis obliterans](#). Circulation. 2010 Apr 27;121(16):1858-61.
84. Piazza G, Creager MA. [Thromboangiitis obliterans](#). Circulation. 2010 Apr 27;121(16):1858-61.
85. O'Dell JR, Linder J, Markin RS, Moore GF. [Thromboangiitis obliterans \(Buerger's disease\) and smokeless tobacco](#). Arthritis Rheum. 1987;30:1054-6
86. Tanaka K. [Pathology and pathogenesis of Buerger's disease](#). Int J Cardiol 1998; 66: 237-42.
87. Dargon PT, Landry GJ. [Buerger's disease](#). Ann Vasc Surg. 2012 Aug;26(6):871-80.
88. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. – Atlanta, GA. : U.S. 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. <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html#>
89. Ohta T, Ishioashi H, Hosaka M, Sugimoto I. [Clinical and social consequences of Buerger's disease](#). J Vasc Surg. 2004 Jan;39(1):176-80.
90. Jiménez-Ruiz CA, Dale LC, Astray Mochales J, et al. [Smoking characteristics and cessation in patients with thromboangiitis obliterans](#). Monaldi Arch Chest Dis. 2006; 65(4):217-21.
91. Mackay A, Brown JJ, Cumming AM, et al. [Smoking and renal artery stenosis](#). Br.Med J 1979; Sep 29;2:770.
92. Stanley JC. [Mesenteric arterial occlusive and aneurysmal disease](#). Cardiol Clin. 2002 Nov;20(4):611-22, vii.
93. Johansson G, Swedenborg J. [Ruptured abdominal aortic aneurysms: a study of incidence and mortality](#). Br J Surgery 1986 Feb;73:101-3.
94. Jenkins A, Ruckley CV, Nolan B. [Ruptured abdominal aortic aneurysm](#). Br J Surgery 1986 May; 73:395-8.
95. Keisler B, Carter C. [Abdominal aortic aneurysm](#). Am Fam Physician. 2015 Apr 15;91(8):538-43.
96. Norman PE, Curci JA. [Understanding the effects of tobacco smoke on the pathogenesis of aortic aneurysm](#). Arterioscler Thromb Vasc Biol. 2013 Jul;33(7):1473-7.
97. Kuivaniemi H, Ryer EJ, Elmore JR, Tromp G. [Understanding the pathogenesis of abdominal aortic aneurysms](#). Expert Rev Cardiovasc Ther. 2015;13(9):975-87.
98. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. – Atlanta, GA. : U.S. 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. <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html#>
99. Moll FL, Powell JT, Fraedrich G, et al. [Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery](#). Eur J Vasc Endovasc Surg. 2011 Jan;41 Suppl 1:S1-S58.
100. Keisler B, Carter C. [Abdominal aortic aneurysm](#). Am Fam Physician. 2015 Apr 15;91(8):538-43.
101. Ahmed R, Ghoorah K, Kunadian V. [Abdominal Aortic Aneurysms and Risk Factors for Adverse Events](#). Cardiol Rev. 2016 Mar-Apr;24(2):88-93.
102. Mackie A for Public Health UK. Public Health Matters. [Abdominal Aortic Aneurysm \(AAA\) Screening Programme - an important milestone](#). January 6, 2016.
103. Mackie A for Public Health UK. Public Health Matters. [Abdominal Aortic Aneurysm \(AAA\) Screening Programme - an important milestone](#). January 6, 2016.

References (continued):

104. NHS Choices. Your health, your choices. [Abdominal aortic aneurysm screening](#). Last reviewed July 24, 2017.
105. Norman PE, Curci JA. [Understanding the effects of tobacco smoke on the pathogenesis of aortic aneurysm](#). *Arterioscler Thromb Vasc Biol*. 2013 Jul;33(7):1473-7.
106. Norman PE, Curci JA. [Understanding the effects of tobacco smoke on the pathogenesis of aortic aneurysm](#). *Arterioscler Thromb Vasc Biol*. 2013 Jul;33(7):1473-7.
107. Norman PE, Powell JT. [Abdominal aortic aneurysm: the prognosis is worse in women than men](#). *Circulation*. 2007 Jun 5;115(22):2865-9.
108. Auerbach O, Garfinkel L. [Atherosclerosis and aneurysm of aorta in relation to smoking habits and age](#). *Chest* 1980 Dec;78:805-9.
109. Forsdahl SH, Singh K, Solberg S, Jacobsen BK. [Risk factors for abdominal aortic aneurysms: a 7-year prospective study: the Tromsø Study, 1994-2001](#). *Circulation*. 2009 Apr 28;119(16):2202-8.
110. Isselbacher E. [Thoracic and abdominal aortic aneurysms](#). *Circulation* 2005 Feb 15;111:816-28.
111. MacSweeney ST, Ellis M, Worrell PC, et al. [Smoking and growth rate of small abdominal aortic aneurysms](#). *Lancet* 1994 Sep 3;344:651-2.
112. Sweeting MJ, Thompson SG, Brown LC, Powell JT; RESCAN Collaborators. [Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms](#). *Br J Surg*. 2012 May;99(5):655-65.
113. Keisler B, Carter C. [Abdominal aortic aneurysm](#). *Am Fam Physician*. 2015 Apr 15;91(8):538-43.
114. Sweeting MJ, Thompson SG, Brown LC, Powell JT; RESCAN Collaborators. [Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms](#). *Br J Surg*. 2012 May;99(5):655-65.
115. Koole D, Moll FL, Buth J, et al; EUROSTAR collaborators. [The influence of smoking on endovascular abdominal aortic aneurysm repair](#). *J Vasc Surg*. 2012 Jun;55(6):1581-6.
116. Norman PE, Curci JA. [Understanding the effects of tobacco smoke on the pathogenesis of aortic aneurysm](#). *Arterioscler Thromb Vasc Biol*. 2013 Jul;33(7):1473-7.
117. Kakafika AI, Mikhailidis DP. [Smoking and aortic diseases](#). *Circ J* 2007 Aug;71:1173-80.
118. Nordon IM, Hinchliffe RJ, Loftus IM, Thompson MM. [Pathophysiology and epidemiology of abdominal aortic aneurysms](#). *Nat Rev Cardiol*. 2011 Feb;8(2):92-102.
119. Garrafa E, Marengoni A, Nave RD, et al. [Association between human parainfluenza virus type 1 and smoking history in patients with an abdominal aortic aneurysm](#). *J Med Virol*. 2013 Jan;85(1):99-104.
120. Wilmink TB, Quick CR, Day NE. [The association between cigarette smoking and abdominal aortic aneurysms](#). *J Vasc Surg*. 1999 Dec;30(6):1099-105.
121. Lottman PE, Van Marrewijk CJ, Fransen GA, et al. [Impact of smoking on endovascular abdominal aortic aneurysm surgery outcome](#). *Eur J Vasc Endovasc Surg*. 2004 May; 27(5):512-8.
122. Khashram M, Williman JA, Hider PN, et al. [Management of Modifiable Vascular Risk Factors Improves Late Survival following Abdominal Aortic Aneurysm Repair: A Systematic Review and Meta-Analysis](#). *Ann Vasc Surg*. 2017 Feb;39:301-311.
123. British Heart Foundation. [Peripheral arterial disease](#). July 31, 2015. London, British Heart Foundation.
124. Peripheral Arterial Disease; NICE CKS, April 2014
125. Meves SH, Diehm C, Berger K, et al. ABI Study Group. [Peripheral arterial disease as an independent predictor for excess stroke morbidity and mortality in primary-care patients: 5-year results of the ABI study](#). *Cerebrovasc Dis*. 2010; 29(6):546-54.
126. Lambert MA, Belch JJ. [Medical management of critical limb ischaemia: where do we stand today?](#) *J Intern Med*. 2013; 274: 295- 307.
127. NICE. [Peripheral Arterial Disease](#). Accessed December 2017.
128. Patient. [Peripheral arterial disease](#). September 21, 2015.
129. Muir RL. [Peripheral arterial disease: Pathophysiology, risk factors, diagnosis, treatment, and prevention](#). *J Vasc Nurs*. 2009 Jun;27(2):26-30.
130. Scientific Committee on Tobacco and Health. [Secondhand Smoke: Review of evidence since 1998](#). November 2004.
131. National Clinical Guideline Centre. [Lower limb peripheral arterial disease: Diagnosis and management](#). NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012.
132. Lightwood JM, Glantz SA. [Declines in acute myocardial infarction after smoke-free laws and individual risk attributable to secondhand smoke](#). *Circulation* 2009 Oct 6;120:1373-1379.
133. Lu L, Mackay DF, Pell JP. [Association between level of exposure to secondhand smoke and peripheral arterial disease: cross-sectional study of 5,686 never smokers](#). *Atherosclerosis*. 2013 Aug;229(2):273-6.
134. Otsuka R, Watanabe H, Hirata K, et al. [Acute effects of passive smoking on the coronary circulation in healthy young adults](#). *JAMA* 2001 Jul 25;286:436-41.
135. Howard G, Wagenknecht LE, Burke GL, et al. [Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities \(ARIC\) Study](#). *JAMA*. 1998 Jan 14;279:119-24.
136. Kritz H, Sinzinger H. [Passive smoking, platelet function and atherosclerosis](#). *Wien Klin Wochenschr*. 1996;108:582-8.
137. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006. https://www.cdc.gov/tobacco/data_statistics/sgr/2006/index.htm
138. Gerhard-Herman MD, Gornik HL, Barrett C, et al. [2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines](#). *Circulation*. 2017 Mar 21;135(12):e686-e725.
139. He Y, Lam TH, Jiang B, et al. [Passive smoking and risk of peripheral arterial disease and ischemic stroke in Chinese women who never smoked](#). *Circulation* 2008 Oct 7;118(15):1535-1540.

References (continued):

140. Lu L, Mackay DF, Pell JP. [Secondhand smoke exposure and intermittent claudication: a Scotland-wide study of 4231 non-smokers](#). Heart. 2013 Sep;99(18):1342-5.
141. Lu L, Jiang C, Mackay DF, et al. [Exposure to secondhand smoke and risk of peripheral arterial disease in southern Chinese non-smokers: The Guangzhou Biobank Cohort Study-Cardiovascular Disease Sub-cohort](#). Vascular. 2017 Jun;25(3):283-289.
142. Lu L, Mackay DF, Pell JP. [Association between level of exposure to secondhand smoke and peripheral arterial disease: Cross-sectional study of 5686 never smokers](#). Atherosclerosis. 2013 Aug;229(2):273-6
143. Agarwal S. [The association of active and passive smoking with peripheral arterial disease: results from NHANES 1999-2004](#). Angiology 2009 Jun-Jul; 60(3):335-345.
144. Morris PB, Ference BA, Jahangir E, et al. [Cardiovascular Effects of Exposure to Cigarette Smoke and Electronic Cigarettes: Clinical Perspectives From the Prevention of Cardiovascular Disease Section Leadership Council and Early Career Councils of the American College of Cardiology](#). J Am Coll Cardiol. 2015 Sep 22;66(12):1378-91.
145. Xua X, Hua H, Kearney G, Kanc H, Shepsa D. [Studying the effects of polycyclic aromatic hydrocarbons on peripheral arterial disease in the United States](#). 1 September 2013, Volumes 461–462, 341-347.
146. Tattersall MC, Johnson HM, Mason PJ. [Contemporary and optimal medical management of peripheral arterial disease](#). Surg Clin North Am. 2013 Aug;93(4):761-78, vii.
147. Peach G, Griffin M, Jones KG, et al. [Diagnosis and management of peripheral arterial disease](#). BMJ. 2012 Aug 14;345:e5208.
148. Patient. [Peripheral arterial disease](#). September 21, 2015.
149. National Clinical Guideline Centre. [Lower limb peripheral arterial disease: Diagnosis and management](#). NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012.
150. European Society of Cardiology. [Diagnosis and Treatment of Peripheral Artery Diseases](#). 2011.
151. Lepantalo M, Lassila R. [Smoking and occlusive peripheral arterial disease](#). Clinical review. Eur J Surg. 1991 Feb;57:83-7
152. Robertson L, Paraskevas KI, Stewart M. [Angioplasty and stenting for peripheral arterial disease of the lower limbs: an overview of Cochrane Reviews](#). Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012542. Published Online: Feb 1, 2017
153. Beard J. [ABC of arterial and venous disease: Chronic lower limb ischaemia](#). BMJ 2000; 320:854-7.
154. Peach G, Griffin M, Jones KG, et al. [Diagnosis and management of peripheral arterial disease](#). BMJ. 2012 Aug 14 345:e5208.
155. Duval S, Long KH, Roy SS, et al. [The Contribution of Tobacco Use to High Health Care Utilization and Medical Costs in Peripheral Artery Disease: A State-Based Cohort Analysis](#). Am Coll Cardiol. 2015 Oct 6;66(14):1566-1574.
156. National Clinical Guideline Centre. [Lower limb peripheral arterial disease: Diagnosis and management](#). NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012.
157. Armstrong EJ, Wu J, Singh GD, et al. [Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease](#). J Vasc Surg. 2014 Dec;60(6):1565-71.
158. Conen D, Everett BM, Kurth T, et al. [Smoking, smoking cessation, \[corrected\] and risk for symptomatic peripheral artery disease in women: a cohort study](#). Ann Intern Med. 2011 June 7;154(11):719-26.
159. Weiss NS. [Cigarette smoking and arteriosclerosis obliterans: an epidemiologic approach](#). Am J Epidemiol 1972 Jan;95:17-25.
160. He Y, Jiang Y, Wang J, et al. [Prevalence of peripheral arterial disease and its association with smoking in a population-based study in Beijing, China](#). J Vasc Surg. 2006 Aug; 44(2):333-8.
161. Alvarez LR, Balibrea JM, Suriñach JM, et al. [FRENA Investigators. Smoking cessation and outcome in stable outpatients with coronary, cerebrovascular, or peripheral artery disease](#). Eur J Prev Cardiol. 2013 Jun;20(3):486-95.
162. Verhaeghe R. [Epidemiology and prognosis of peripheral obliterative arteriopathy](#). Drugs. 1998;56 Suppl 3:1-10.
163. Krupski WC. [The peripheral vascular consequences of smoking](#). Ann Vasc Surg. 1991 May;5(3):291-304.
164. He Y, Jiang Y, Wang J, et al. [Prevalence of peripheral arterial disease and its association with smoking in a population-based study in Beijing, China](#). J Vasc Surg. 2006 Aug; 44(2):333-8.
165. Girolami B, Bernardi E, Prins MH, et al. [Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: A meta-analysis](#). Arch Intern Med. 1999 Feb 22;159(4):337-45.
166. Krupski WC. [The peripheral vascular consequences of smoking](#). Ann Vasc Surg. 1991 May;5(3):291-304.
167. Juergens JL, Barker NW, Hines EA. [Arteriosclerosis obliterans: a review of 520 cases with special reference to pathogenic and prognostic factors](#). Circulation 1960 Feb;21:188-95.
168. Patterson A, Clarke F. Vascular disease. Pulse. 1993;69-73.
169. Wiseman S, Kenchington G, Dain R, et al. [Influence of smoking and plasma factors on patency of femoropopliteal vein grafts](#). BMJ 1989 Sep 9;299:643-6.
170. Birkenstock WE, Louw JH, Terblanche J, et al. [Smoking and other factors affecting the conservative management of peripheral vascular diseases](#). S Afr Med J. 1975 Jul 5;49(28):1129-32
171. National Clinical Guideline Centre. [Lower limb peripheral arterial disease: Diagnosis and management](#). NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012.
172. Gerhard-Herman MD, Gornik HL, Barrett C, et al. [2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines](#). Circulation. 2017 Mar 21;135(12):e686-e725.
173. Rooke TW, Hirsch AT, Misra S, et al. [Management of patients with peripheral artery disease \(compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations\): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines](#). J Am Coll Cardiol. 2013 Apr 9;61(14):1555-70.

References (continued):

174. Bonaca MP, Creager MA. [Pharmacological treatment and current management of peripheral artery disease](#). Circ Res. 2015 Apr 24;116(9):1579-98.
175. Klein-Weigel P, Volz TS, Zange L, Richter J. [Buerger's disease: providing integrated care](#). J Multidiscip Healthc. 2016 Oct 12;9:511-518. eCollection 2016.
176. Katsiki N1, Papadopoulou SK, Fachantidou AI, Mikhailidis DP. [Smoking and vascular risk: are all forms of smoking harmful to all types of vascular disease?](#) Public Health. 2013 May;127(5):435-41.
177. National Clinical Guideline Centre. [Lower limb peripheral arterial disease: Diagnosis and management](#). NICE Clinical Guideline 147. Methods, evidence and recommendations. August 2012.
178. Aboyans V, Ricco JB, Bartelink MEL, et al. [2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery \(ESVS\)](#). Eur J Vasc Endovasc Surg. 2017 Aug 26.
179. Steinberg MB, Greenhaus S, Schmelzer AC, et al. [Triple-combination pharmacotherapy for medically ill smokers: a randomized trial](#). Ann Intern Med 2009 Apr 7;150(7):447-454.
180. Aboyans V, Thomas D, Lacroix P. [The cardiologist and smoking cessation](#). Curr Opin Cardiol 2010 Sep;25(5):469-477.
181. Aboyans V, Ricco JB, Bartelink MEL, et al. [2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery \(ESVS\)](#). Eur J Vasc Endovasc Surg. 2017 Aug 26.
182. Rooke TW, Hirsch AT, Misra S, et al. [Management of patients with peripheral artery disease \(compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations\): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines](#). J Am Coll Cardiol. 2013 Apr 9;61(14):1555-70.
183. Goodney PP, Spangler EL, Newhall K, et al. [Feasibility and pilot efficacy of a brief smoking cessation intervention delivered by vascular surgeons in the Vascular Physician Offer and Report \(VAPOR\) Trial](#). J Vasc Surg. 2017 Apr;65(4):1152-1160.e2.
184. Newhall K, Suckow B, Spangler E, et al. [Impact and Duration of Brief Surgeon-Delivered Smoking Cessation Advice on Attitudes Regarding Nicotine Dependence and Tobacco Harms for Patients with Peripheral Arterial Disease](#). Ann Vasc Surg. 2017 Jan;38:113-121.
185. Henrikus D, Joseph AM, Lando HA, et al. [Effectiveness of a smoking cessation program for peripheral artery disease patients: a randomized controlled trial](#). J Am Coll Cardiol. 2010 Dec 14;56(25):2105-12.
186. Katsiki N1, Papadopoulou SK, Fachantidou AI, Mikhailidis DP. [Smoking and vascular risk: are all forms of smoking harmful to all types of vascular disease?](#) Public Health. 2013 May;127(5):435-41.
187. Aggarwal S, Loomba RS, Arora R. [Preventive aspects in peripheral artery disease](#). Ther Adv Cardiovasc Dis. 2012 Apr;6(2):53-70.
188. NICE. [Peripheral arterial disease: diagnosis and management](#). August 2012.