Smoking Cessation in Patients with Cardiovascular Disease: An Expert Panel

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Around 7 million people in the UK are living with cardiovascular disease (CVD). It's responsible for 25% of all deaths – over 150,000 deaths each year in the UK, 42,000 of these are in people under 75 years of age. CVD costs the NHS an estimated £9 billion, and costs the UK economy an estimated £19 billion each year [(1)]. Coronary heart disease (CHD) is the most common form of CVD, and is one of the UK's leading causes of death, accounting for 66,000 deaths per year – around a third of these in people under 75 years of age. It is the leading cause of death worldwide. There are 2.3 million people living with CHD in the UK [(1)].

In January 2019, a panel of three cardiologists with an interest in smoking cessation met to discuss the issues surrounding this important part of risk factor modification. Are cardiologists doing enough to help their patients stop smoking? What more could they be doing?

Why is smoking cessation an increasingly important therapeutic goal for patients with cardiovascular disease?

Nearly one in six adults in the UK smoke cigarettes, and it's estimated that around 20,000 deaths in the UK each year from heart and circulatory diseases can be attributed to smoking [(1)].

Cigarette smoking is a significant risk factor for CVD. Smoking predisposes individuals to several different atherosclerotic syndromes, including stable angina, acute coronary syndrome, sudden death, and stroke. Aortic and peripheral atherosclerosis lead to abdominal aortic aneurysms and intermittent claudication [(2)].

Even occasional smoking poses significant risks. A 2019 US study [(3)] of over seventy thousand people found that lifelong non-daily smokers (median 50 cigarettes per month) had a 72% higher mortality risk compared to never smokers. Even those who reported 11-30 cigarettes per month had a 34% higher risk. Life expectancy was around 5 years shorter for lifelong non-daily smokers.

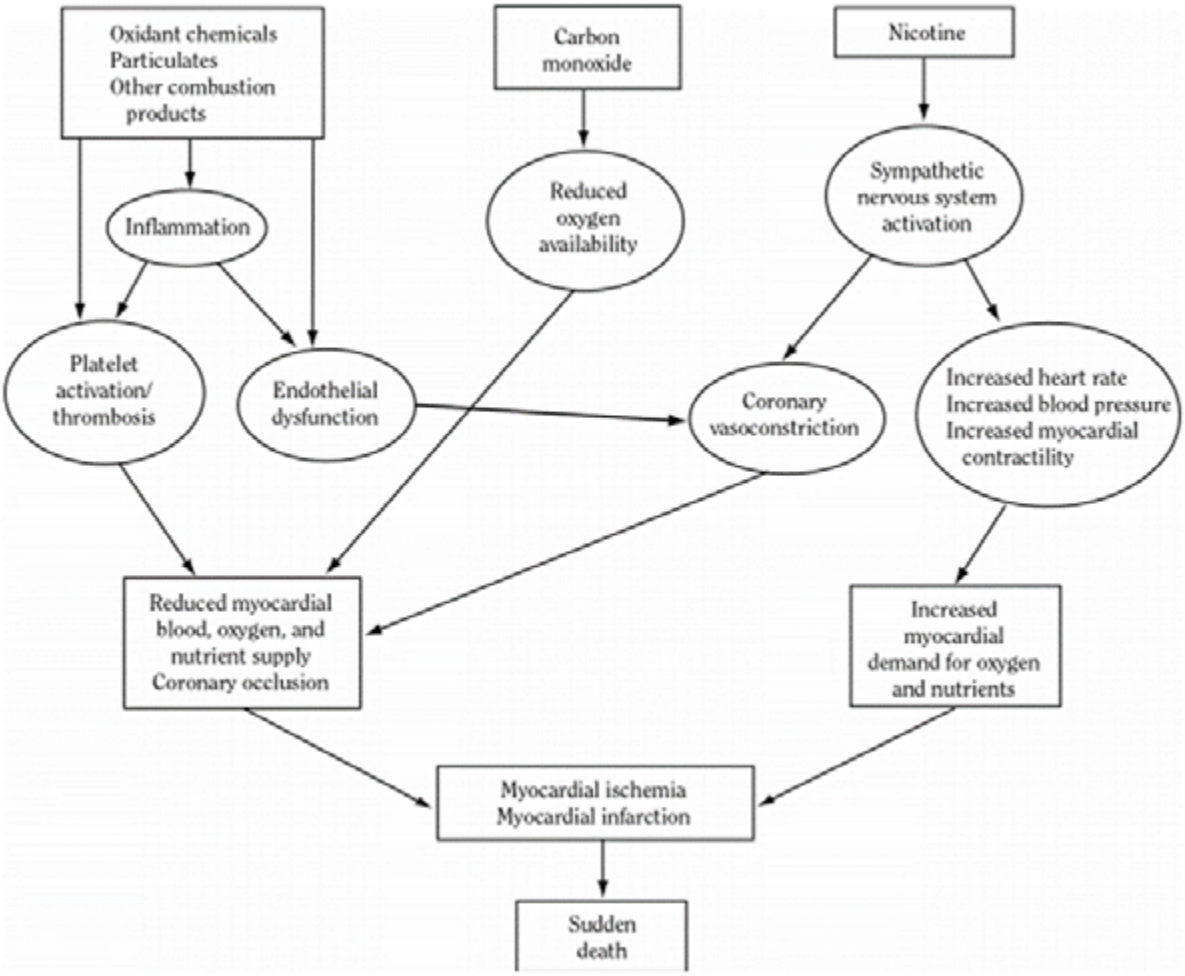
Cigarette smoke contains many harmful chemicals. Nicotine activates the sympathetic nervous system, increasing heart rate, blood pressure, and myocardial contractility, thereby increasing myocardial demand for oxygen and nutrients. However, while nicotine is commonly implicated in the increase in CVD with smoking, tolerance appears to develop to most of these effects. Furthermore, use of nicotine replacement treatments does not appear to increase CVD other than mild forms of tachyarrhythmia [(4,5)].

Carbon monoxide binds with haemoglobin, reducing oxygen delivery to tissues. The resultant functional anaemia increases thrombogenesis and thrombocytosis. Oxidant chemicals and particulates cause inflammation, platelet activation with hyper-coagulation, and endothelial dysfunction leading to coronary vasoconstriction. The result of these processes is increased myocardial demand for oxygen and nutrients, which is met with decreased myocardial blood, oxygen and nutrient supply. The mismatch promotes myocardial ischaemia and infarction [(6)]. *Figure 1* summarises these mechanisms.

Do e-cigarettes cause similar risks as smoking?

E-cigarettes deliver nicotine by heating and vaporising a nicotine-containing solution, which is inhaled or 'vaped' by the user. Liquids are typically flavoured and contain varying concentrations of nicotine. An important distinction between traditional cigarettes and e-cigarettes is the lack of carbon monoxide in the latter, and therefore the absence of the resultant functional anaemia.

Figure 1: Overview of mechanisms by which cigarette smoking causes an acute cardiovascular event



Source: Benowitz. Trends Cardiovasc Med. 2016 Aug; 26(6): 515–523. (7)

Evidence of the acute cardiovascular effects of e-cigarettes are so far consistent with the expected effects of nicotine, and no long-term data is available on the effects in people with CVD. A 2017 literature review [8] indicates that e-cigarette use might pose some cardiovascular risk, particularly in those with existing CVD. But the risk is thought to be lower than that of cigarette smoking.

In what way is cigarette smoking integrated in CVD risk assessment? Calculating and communicating the ten year CVD risk plays an essential role in patient management, and is recommended by the National Institute for Health and Care Excellence (NICE) [9]. CVD risk assessment tools, such as QRISK®, are widely available and take into account a number of cardiovascular risk factors, but only provide an estimate of risk. Understanding a patient's risk factors and ten year CVD risk enables tailored treatment strategies to be implemented, at the earliest opportunity in order to achieve the best long-term outcomes for each patient. Smoking cessation would move large numbers of patients into lower risk groups that would not require further medical treatment, for example with statins, to lower their CVD risks. However, complete cessation is needed for risk to be lowered.

What are the benefits of complete smoking cessation when compared to alternatives such as e-cigarettes?

Among British current and former smokers, the most commonly given reasons for vaping were perceived health benefits compared to traditional cigarettes, and as an aid to smoking cessation [10].

The NHS advises that research shows that e-cigarettes can help you give up smoking [11]. The NHS Smokefree webpage reports that of the estimated 2.9 million adults in Great Britain who currently use e-cigarettes, 1.5 million have completely stopped smoking cigarettes [12]. In the year up to April 2015, 2 out of 3 people who used e-cigarettes in combination with the NHS stop smoking service quit smoking successfully [11].

A 2018 literature review concluded there is a reduction in traditional cigarette use in those who regularly use e-cigarettes, and e-cigarettes have less acute toxic effects [13]. However, the same review also noted that randomised controlled trials (RCTs) have not demonstrated that e-cigarettes are an effective tool for smoking cessation, whereas results from cohort studies are conflicting. Although e-cigarette use reduces traditional cigarette consumption, this reduction does not correlate with increased

cessation [13] and the risk of CVD remains high as long as some usual cigarettes are smoked. As e-cigarettes are still fairly new, long-term safety has not been completely established. Clinicians are encouraged to report safety concerns via the Yellow Card Scheme [11].

Since publication of these reviews and meta-analyses, a randomized controlled trial conducted among smokers attending UK National Health Service stop-smoking services compared use of nicotine-replacement products, including combinations, to e-cigarettes with 18 mg/ml of nicotine for smoking cessation [14]. Both groups were given weekly behavioural support for at least 4 weeks. The study showed that one year abstinence rates were higher with e-cigarettes compared to NRT, 18.0% vs 9.9% (relative risk 1.83; 95% confidence interval 1.30 to 2.58, p<0.001). Of those who achieved one year abstinence, 80% of those in the e-cigarette group and 9% in the NRT group were still using the assigned product at one year. If e-cigarettes are to be used, they should be vaped on a short-term basis as a tool for cessation, not as a long-term replacement for cigarettes. Furthermore, it is highly unlikely that dual users – those who smoke cigarettes and use e-cigarettes – would see any health benefits, so this approach cannot be recommended.

Is there current data which supports the safety and efficacy of smoking cessation drugs?

There are three pharmacotherapies available for smoking cessation: varenicline, bupropion and NRT.

Varenicline (Champix) is recommended by NICE as an option for smokers who have expressed a desire to quit smoking as part of a programme of behavioural support [15]. A nicotine receptor partial agonist, it both alleviates symptoms of craving and withdrawal, and reduces the rewarding and reinforcing effects of smoking. Treatment should start 1 to 2 weeks before smoking cessation.

In a 2016 Cochrane review [16], a pooled analysis of 27 trials of 12,625 patients found that varenicline at standard dosage versus placebo had a risk ratio (RR) of 2.24 (95% CI 2.06 to 2.43) for continuous or sustained abstinence at 6 months or longer. The pooled RR for varenicline versus bupropion at six months was 1.39 (95% CI 1.25 to 1.54; 5 trials, 5877 people). The RR for varenicline versus NRT for abstinence at 24 weeks was 1.25 (95% CI 1.14 to 1.37; 8 trials, 6264 people). The most frequently reported adverse effect was nausea, which was mostly mild to moderate in severity and usually subsided over time [16]. Other very common adverse effects of varenicline include nasopharyngitis, abnormal dreams, insomnia, and headache [17]. There was early concern about the possibility of an increased risk of cardiovascular events, but a 2016 systematic review and meta-analysis [18] found no evidence of this, in patients with and without CVD.

Bupropion is a centrally-acting noradrenaline and dopamine reuptake inhibitor. A 2013 Cochrane review [19] found bupropion to be superior to placebo with an odds ratio (OR) for cessation of 1.82 (95% credible interval [CredI] 1.60 to 2.06). Head-to-head comparisons between bupropion and NRT showed equal efficacy (OR 0.99; 95% CredI 0.86 to 1.13). Pooled analysis of serious adverse events showed no excess of neuropsychiatric or cardiovascular events [19]. The most frequently reported adverse effect is insomnia, and there is around a 1/1000 risk of seizure [20].

There was early concern over the neuropsychiatric safety of varenicline and bupropion. The EAGLES trial [21] was a large, multi-national, randomised, placebo- and active-controlled trial of over eight thousand smokers, with and without psychiatric disorders. It found no significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion compared with nicotine patch or placebo. The trial has allayed any psychiatric safety concerns. Neuropsychiatric and abstinence outcomes are summarised in *Table 2*.

NRT comes in a variety of forms: gum, patches, lozenges, microtabs, inhalators, nasal sprays, and oral sprays. A Cochrane review [22] of 133 trails in 64,640 patients found the overall RR of abstinence for any form of NRT relative to control (placebo or no-NRT) to be 1.55 (95% CI 4.49 to 1.61). Results from subgroup analysis on the different forms of NRT are shown in *Table 1*.

Furthermore, combining NRT treatments (using patches and lozenges for example) outperformed using single formulations [19]. Combination use of NRT may be as effective as varenicline [19].

Adverse events were related to the type of product, and included skin irritation from patches, and mouth irritation from gum and tablets. The odds ratio of chest pain or palpitations for any form of NRT was 1.88 (95% CI 1.37 to 2.57), but these symptoms were rare in both groups, and serious adverse events were very rare.

Table 1: Subgroup analysis on efficacy of different formulations of NRT

Preparation	Risk ratio for abstinence (95% CI)	
Gum	1.49	(1.40 – 1.60)
Patch	1.64	(1.53 – 1.75)
Tablet/lozenge	1.52	(1.32 – 1.74)
Inhalator	1.90	(1.36 – 2.67)
Nasal spray	2.02	(1.49 – 2.73)
Oral spray	2.48	(1.24 – 4.94)

The 2016 Joint European Societies (JES) Guidelines on cardiovascular disease prevention in clinical practice [23] recognise the strong evidence base for varenicline, bupropion and all forms of NRT. They recommend brief interventions plus assistance with stopping using drug therapy and follow-up.

The EUROASPIRE study (2019) [24] interviewed over 8,000 patients in 27 countries ≥6 months after their verified coronary artery events or interventions. The purpose was to examine whether the JES guidelines on secondary cardiovascular prevention [23] were being followed. 19% of these patients smoked, and the prevalence of persistent smoking – defined as smoking at the time of interview

Table 1: (Summary of neuropsychiatric and abstinence outcomes from EAGLES trial (21)

	Non-psychiatric cohort				Psychiatric cohort			
	Varen.	**Bupro.**	**NP**	**Placebo**	**Varen.**	**Bupro.**	**NP**	**Placebo**
Primary composite neuropsychiatric endpoint (%)	1.3	2.2	2.5	2.4	6.5	6.7	5.2	4.9
Estimated primary composite neuropsychiatric adverse events (% [95% CI])	1.25 (0.60 to 1.90)	2.44 (1.52 to 3.36)	2.31 (1.37 to 3.25)	2.52 (1.28 to 3.46)	6.42 (4.91 to 7.93)	6.62 (5.09 to 8.15)	5.20 (3.84 to 6.56)	4.83 (3.51 to 6.16)
Difference in risk of composite primary endpoint (RD% [95% CI])								
Versus placebo	−1·28 (−2·40 to −0·15)	−0·08 (−1·37 to 1·21)	−0·21 (−1·54 to 1·12)	--	1·59 (−0·42 to 3·59)	1·78 (−0·24 to 3·81)	0·37 (−1·53 to 2·26)	--
Versus nicotine patch	−1·07 (−2·21 to 0·08)	0·13 (−1·19 to 1·45)	--	--	1·22 (−0·81 to 3·25)	1·42 (−0·63 to 3·46)	--	--
Versus bupropion	−1·19 (−2·30 to −0·09)	--	--	--	−0·20 (−2·34 to 1·95)	--	--	--
Continuous abstinence rates (%)								
Weeks 9-12	38.0	26.1	26.4	13.7	29.2	19.3	20.4	11.4
Weeks 9-24	25.5	18.8	18.5	10.5	18.3	13.7	13.0	8.3

Varen. = Varenicline **Bupro.** = Bupropion **NP** = Nicotine patch **CI** = Confidence interval **RD** = Risk difference

varenicline, bupropion and NRT were prescribed to only 2%, 1% and 7% of smokers respectively. Of further concern, 53% of persistent among those who smoked in the month prior to the index cardiac event, was 55%. Although 85% of persistent smokers had been offered professional advice to quit, just 23% had actually tried to stop, with only 5% having attended a smoking cessation clinic. Pharmacological cessation aids in the form of smokers interviewed did not have the intention to quit within the next 6 months.

The INTERHEART study (2004) [25] was a large standardised case-control study looking at the effect of potentially modifiable risk factors associated with acute myocardial infarction (MI). Around 30,000 patients from 52 countries were enrolled and the odds ratios (OR) and population attributable risks (PAR) for various risk factors were reported. PAR is the proportion of the incidence of a disease (MI) in the population that is due to exposure (smoking), or in other words the incidence of a disease in the population that would be eliminated if exposure were eliminated. Smoking was found to have an odds ratio of 2.87 for current vs never smokers, and a PAR of 35.7% for current and former vs never smokers.

How has the availability of pharmacological smoking cessation aids and the data from key studies influenced the way in which you manage patients?

The paradigm has shifted significantly since the introduction of pharmacological aids. Common practice used to involve asking the patient about smoking and advising them to quit. Now health care professionals including cardiologists may clearly inform the smoker that "we have treatments that can help you quit".

The 3A's model [26] provides a structure for delivering very brief advice (VBA) to smokers, and can be performed by any healthcare professional. This intervention can be delivered in as little as 30 seconds, and is recommended by NICE [27]. It consists of:

- Ask and record smoking status
- Advise on the best way of quitting – combination of medication and specialist support
- Act on the patients response – build confidence, give support, refer and prescribe

Training on delivering very brief advice is available via the National Centre for Smoking Cessation and Training (NCSCT) [28].

This approach reduces some of the lack of self-efficacy in smokers that they would not be able to quit successfully.

Efficacy and safety of cessation treatments has been demonstrated from numerous large trials and meta-analyses. Cardiovascular safety of varenicline, bupropion and NRT has been assessed in a recent publication from the EAGLES trial [29]. No evidence was found that any of the smoking cessation pharmacotherapies increased the risk of serious cardiovascular adverse events during or after treatment.

Patients recognise that quitting will be hard, and may want to postpone. Confidently offering proven therapies that will help with their symptoms of withdrawal and increase their chances of successfully quitting is enormously beneficial.

For patients who are reluctant to add another medication, it can help to emphasise that unlike the other medications they are on, smoking cessation treatments are short term.

How can physicians best determine how and when to implement smoking cessation strategies/interventions?

Smoking is the most important of the modifiable cardiac risk factors in patients with CVD, and smoking cessation is the most important secondary prevention strategy [30].

The Ottawa Model for Smoking Cessation (OMSC) is a multicomponent intervention strategy, originally developed for cardiac inpatients [31], and has now been adapted to outpatient and primary care settings. It consists of:

1. Identifying smokers on admission
2. Documenting smoking status in patient records
3. Providing smokers with advise and behavioural support to quit
4. Offering smoking cessation medications during their hospital stay
5. Offering follow-up support on discharge

Follow up is monitored by an automated, interactive voice response (IVR) system that tracks patients for up to six months. Patients who report difficulties in their cessation efforts are contacted by relevant staff [32].

Implementing the OMSC has been shown to increase smoking cessation rates in the inpatient [33] setting.

Hospitalisation provides a good opportunity for smoking cessation. Patients admitted for treatment of smoking-related diseases can be highly motivated to quit, and UK hospitals are smoke-free environments [34]. Initiating smoking cessation interventions during hospitalisation may help more people successfully quit [35].

A 2008 Cochrane Review [35] looking at smoking cessation interventions in hospitalised patients found that intensive counselling interventions that began in the inpatient setting and continued with supportive contacts for at least one month after discharge increased smoking cessation rates by 65%. Similarly, in the subset of patients admitted for CVD, similar intervention with follow-up support increased the odds of smoking cessation by 81%. Less intensive interventions and shorter follow up periods have not been shown to be beneficial.

One trial from the review [36] showed that hospital smoking cessation intervention and follow up for at least a month, in patients with CVD, produced a relative risk reduction of 0.77 in all-cause mortality, and a relative risk reduction of 0.44 in hospital readmissions over a 2-year follow-up.

NICE recommends smokers should be identified during inpatient admissions, and help to stop should be offered, with information, intensive support referral and pharmacological interventions. Referral to community stop smoking services should be made at discharge [37].

At each hospital level what should be done?

Smoking cessation pharmacotherapies should be offered on the first day of admission for acute coronary syndrome. It should be noted that at this stage, many patients may feel motivated to quit without any pharmacological support, so a discussion about the benefits of treatments is key. Cessation needs to be discussed again prior to discharge, as resumption of normal life causes significant relapse rates. The agreed smoking cessation plan should be clearly documented in the medical notes and on the discharge summary, along with a referral to community stop smoking services.

Clear documentation of cessation strategies on the discharge summary is of paramount importance. There may be anxiety in primary care to start a new medication that the cardiologist hasn't approved, on top of the other treatments that have been started in hospital.

Many patients who quit while in hospital, start smoking again after discharge. Rehabilitation offers a further valuable opportunity to impart knowledge and engage patients in cessation. Cardiac rehabilitation settings are ideal for the delivery of comprehensive smoking cessation programmes [30]. Pharmacotherapies should again be offered to those not taking them. Smoking cessation should be a priority in this setting as it's the single most valuable facet of secondary prevention.

In the outpatient setting, patients are likely to have already been given a lot of advice, and so information giving at this stage is not likely to be a priority. Here, offering treatment, and agreeing on a robust cessation plan for those who are still smoking is the priority. Lifestyle related secondary prevention strategies should begin with smoking cessation; diet and exercise can be addressed later. A

quit date should be agreed upon, sometime in the next 4-8 weeks, avoiding times where cessation will be most difficult. Treatments should begin at the appropriate time before the quit date, and patients should be advised to smoke as much as they want before the quit date.

What can we learn from the Ottawa model for smoking cessation?

Routine screening to identify smokers and documentation is paramount and can be done by any healthcare professional. Hospitalisation, especially for a smoking-related disease or event, provides an opportune time for smoking cessation, and this opportunity should not be wasted. Following a standardised treatment approach, such as the OMSC, overcomes time pressure on the part of the physician as a barrier. Referral and initiation of intensive behavioural support while in hospital is effective. Discussion and provision of cessation pharmacotherapies is safe and effective.

Follow-up is key and referral to community stop smoking services is essential. Seamless transition between secondary and community smoking cessation services is the ideal. Ongoing support and follow-up in the community is effective when provided by adequately trained staff. Monitoring of smoking cessation in the community can be automated, with human contact provided only when needed.

What criteria do you use to determine the optimal therapy to a patient's existing treatment regimen?

Varenicline has been shown to be the most effective pharmacotherapy [16] and so is often the first line treatment. Nausea and abnormal dreams/sleep disturbance are two of the most common side effects. Patients can be counselled to take the tablets with food to help with nausea, and to take the evening dose early in the evening rather than immediately before bed.

Bupropion is contraindicated in patients with a risk of seizures, eating disorders or dipolar disorder, so these need to be screened for. However, it remains an effective treatment for a wide range of smokers.

Many patients will have previously tried NRT, but this does not rule its subsequent use. Often they will not have used a high enough dose, or may not have used it for long enough. A patch can provide the baseline nicotine replacement, along with a short-acting preparation including mouth spray, gum or inhaler used as needed to deal with breakthrough cravings. While combinations of e-cigarettes with established smoking cessation drugs have not been studied, the combination may be effective in some very hard to treat patients (personal experience).

Side effects profiles, contraindications and patient preferences should be taken into account when agreeing on the optimal treatment strategy.

The ability to combine pharmacological interventions is helpful. A 2014 RCT [38] compared varenicline combined with NRT to varenicline alone, and demonstrated a higher cessation rate with combination treatment at 12 weeks (OR 1.85) and at 24 weeks (OR 1.98). This finding was confirmed in a 2015 meta-analysis of three RCTs [39]. However, RCTs have showed no difference in combining bupropion with NRT compared to bupropion alone [40,41,42].

Varenicline treatment is recommended for 12-24 weeks [17]. Bupropion treatment lasts 7-9 weeks [20]. Both treatments include dose titration in the first week, and both should ideally be started 1-2 weeks prior to stopping smoking. The various forms of NRT come with a range of recommended dosing schedules.

From your perspective, what are the main advantages of the early use of a smoking cessation drug?

Patients are highly motivated after a CV event, and hospital admission provides a 'teachable moment' for many patients. This opportunity should not be squandered. Cessation results in greater reductions in CVD mortality than any other secondary prevention intervention [43]. Furthermore, the benefits of lipid lowering and antihypertensive drugs are significantly reduced in those who smoke [43]. As the most important facet of secondary prevention, smoking cessation should not be postponed. In the first year after cessation, mortality rates reduce by half, [44] so there are real benefits to early cessation. It is difficult to find valid reasons to delay cessation, for the patient or the health service.

Prolonging life may not work as a motivation for some patients for a variety of reasons. Focussing on healthy years of life may be more beneficial in these cases – avoiding amputations, stents and the need for oxygen therapy.

How has the availability of smoking cessation drugs improved the lives of your patients?

There is an abundance of high quality evidence demonstrating the efficacy and safety of pharmacological interventions for smoking cessation, and these treatments need to be made routinely available to patients who come into contact with healthcare professionals. Smokers typically experience feelings of shame about their smoking, particularly those who've had a cardiac event. In practice, it is more effective to focus on the benefits of quitting rather than to increase their levels of shame about smoking.

It was previously widely believed that the benefits of smoking cessation only became apparent after many years. However, this is not accurate. In practice, patients who have successfully quit notice an improvement in their breathing within a few days. Blood pressure and heart rate also frequently lower in this time. Patients feel healthier and are proud of their achievement. They enjoy a demonstrably lower CV risk. There are significant financial savings, and they are pleased that they no longer need to spend time every day making arrangements to smoke in an increasingly smoke-averse society. Furthermore, unlike blood pressure and

lipid treatments which only benefit the patient, smoking cessation treatments potentially benefit the entire family through reduction in passive smoking. In fact, people exposed to second hand smoke have a 20-30% increased risk of morbidity and mortality associated with CHD [43].

CONCLUSION

Smoking cessation offers greater reductions in CVD mortality than any other secondary prevention measure. Hospitalisation for a smoking-related disease or event provides an ideal opportunity for cessation. Varenicline, bupropion and NRT have all been shown to be effective when combined with behavioural support. Their safety profiles are reassuring. Smoking cessation should therefore be treated as a top priority by all professionals treating and caring for patients with CVD, with routine initiation of pharmacotherapies in the hospital setting.

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