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Aspirin for the older person: report of a meeting at the Royal Society of Medicine, London, 3rd November 2011

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Conference Report

Abstract

On November 23rd 2011, the Aspirin Foundation held a meeting at the Royal Society of Medicine in London to review current thinking on the potential role of aspirin in preventing cardiovascular disease and reducing the risk of cancer in older people. The meeting was supported by Bayer Pharma AG and Novacy1.

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Introduction

P Elwood

Professor Peter Elwood, Honorary Professor in Primary Care and Director of Primary Care and Public Health, University of Cardiff, was one of the investigators in the first trial of aspirin for the prevention of cardiovascular events [1]. His interest in the role of aspirin in cancer prevention was sparked by a botanist colleague, who pointed out that plants express salicylic acid in response to cancer cells. Why has not this phenomenon been explored in humans, the botanist asked? Since that time, many observational studies have reported an association between aspirin intake and reduced cancer risk but, in 2010, convincing evidence from long-term follow-up from prospective randomised trials showed that aspirin reduced the risk of death from cancer, and from colorectal cancer in particular [2,3]. Most recently, the CAPP2 trial demonstrated that aspirin reduces the incidence of cancer in people with Lynch syndrome, who are at increased risk of bowel cancer [4]. Despite some reservations, Professor Elwood said, there is now no reasonable doubt about the preventative effects of aspirin.

Society has a poor record of adopting risk reduction strategies. For example, US studies show that the five healthy behaviours (exercise, healthy diet, maintain low body weight, no smoking, modest alcohol use) can reduce heart disease by 80–85 per cent but adherence to these lifestyle measures (in the context of the trials) was only 3–4 per cent [5,6]. In Wales, the 1980 Caerphilly Cohort Study followed up 2,500 men for 30 years and demonstrated progressive reductions in the risks of death, vascular disease and diabetes as more protective lifestyle measures were adopted – but only 1.5 per cent of men adhered to all five healthy behaviours [7].

People do not adopt preventive measures which bring great benefit to the population because they offer little to each individual [8]. Taking aspirin daily is, by contrast, a simple measure and there is a risk that it could be perceived as a substitute for healthy behaviours because it is an easier option. In Wales, 36 per cent of the over-50s already take regular aspirin. Professor Elwood suggested that the public has acted, leaving health professionals and health authorities behind.

The question now facing society is, Who has responsibility for ensuring the appropriate use of aspirin? The treatment of disease has been delegated to health professionals, Professor Elwood said. His belief is that individuals should be given valid evidence on the balance of risks and benefits, and decide for themselves whether to take aspirin.

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Update on aspirin and cancer prevention

J Cuzick

In 2009, an international consensus statement on the role of aspirin and NSAIDs for cancer prevention concluded that there was clear evidence of a chemopreventive effect on colorectal cancer and probably other cancer types but there were insufficient data on the risk-benefit profile; as a result, no definitive recommendations were made-(Professor Jack Cuzick, Professor of Epidemiology at Cancer Research UK) [1].

And lead author of that paper, said that much new evidence has since been published; the consensus statement is being updated and will be published in 2012.

Professor Cuzick described recent evidence from prospective trials that aspirin reduced cancer mortality as very important. This analysis, published in 2010, involved approximately 25,000 people and identified about 600 deaths [2,3]. It showed that daily aspirin reduced the risk of cancer mortality by 21 per cent - but the effect was seen only after a delay of 5 years. The biggest effect was on gastrointestinal cancers, with potential effects on cancers at other sites. Although there are concerns that some trials had been inappropriately excluded, this analysis provides strong evidence.

The first evidence that NSAIDs might protect against colorectal cancer was a 1983 case series in which sulindac reduced the incidence of colorectal polyps in individuals with Gardner's syndrome [4]. Twenty years later the first randomised trial demonstrated that aspirin reduced by 35 per cent the risk of colorectal adenoma in patients with a history of colorectal cancer although only after 5 years' use [5]. Case control and cohort studies have consistently shown a reduction in the risk of colorectal cancer associated with aspirin use [6]. Taking aspirin after a diagnosis of colorectal cancer is associated with a lower cancer-specific and overall mortality [7] but this is a relatively rapid effect and therefore probably due to another mechanism, such as inhibition of COX-2 in tumours over-expressing this enzyme. In the CAPP2 trial, daily aspirin reduced the incidence of colorectal cancer by 37 per cent overall in people with Lynch syndrome, and by 60 per cent in those who adhered to treatment for at least 2 years [8]. Again, this benefit was evident only after 5 years (Figure 1) – unusual in a high-risk population such as this, Professor Cuzick commented, contrasting it with the immediate benefit of anti-hormone therapy in women with breast cancer.

Observational studies have also found that that regular aspirin use was associated with 10–30 per cent reductions in the risk of cancers of the oesophagus, stomach and breast, and probably a lesser effect on the risk of cancers of the lung and prostate. The Nurse's Health Study further showed that current aspirin use is associated with a 40–60 per cent lower risk of breast cancer recurrence [9]. There is less certainty about the effects of aspirin in reducing the risk of other cancers, with conflicting data for ovarian cancer and no evidence of a benefit in pancreatic cancer.

Professor Cuzick noted that several questions about aspirin remain unanswered. Which is the appropriate dose – 75 mg/day or 300 mg/day? Prospective studies [2,3] did not find a dose-response effect, he said, though alternate-day dosing had been excluded from this analysis. Studies are needed to address this question. Is it sufficient to take aspirin for 5 years and then stop, or should we continue? Which are the best ages to start and stop aspirin? It appears that gastrointestinal bleeding is a serious risk predominantly in the over-70s - is 65–70 therefore the age to stop? There is growing evidence that many patients with gastrointestinal bleeding are *Helicobacter pylori* positive: should individuals be tested and treated before starting aspirin? How important are genetic factors? Much of the evidence of the

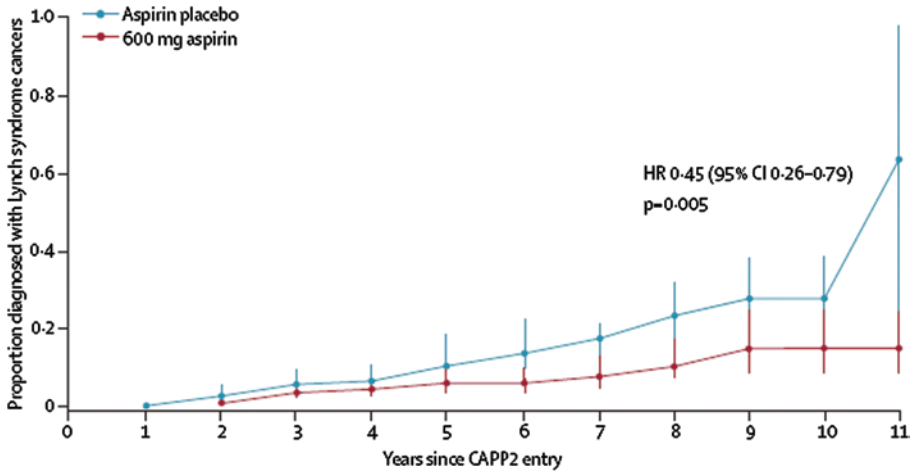

Figure 1: Delayed reduction in the risk of colorectal cancer in the CAPP2 trial [8]. Reproduced with kind permission from The Lancet.

benefits of aspirin come from studies in men whereas the benefits in women have been inconsistent. This was due to negative results from the Women's Health Study and longer follow-up of this cohort is awaited

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Aspirin and cancer – the views of the patients

K Spencer

Europacolon (www.europacolon.com) is a pan-European patient advocacy organisation founded in 2005. It aims to unite patients, carers, healthcare professionals, politicians, the media and the public in the fight against colorectal cancer. Its goals are, explained Keith Spencer, Director of Special Projects: to create a European colorectal cancer community; to ensure formal population screening and availability, improved choice and equitable access to best treatment and care throughout Europe; and to ensure the continued implementation of conformity to EU recommendations, guidelines and policy. Patient advocacy operates at two levels, promoting awareness among the public and people with colorectal cancer, and lobbying to influence policy makers and health professionals.

Mr Spencer said the public is aware that interesting claims are being made that aspirin may reduce cancer risk and prolong survival. Where will they get their information about it? GPs seem more concerned by the possible risks of aspirin than its potential benefits and they are not particularly well informed about recent evidence. Media coverage is transitory and usually adopts a sensational perspective angle, emphasising headlines at the expense of detail. The Internet, of course, is an easy way to do research but it is full of anecdotal comment. It has an excess of information, much of which is contradictory, not easily understandable and possibly even frightening. It is easy to come away with the impression that taking aspirin is dangerous, Mr Spencer noted.

The public generally do not know enough about the risks and benefits of aspirin, or they do not understand the issues, he continued. Relevant studies should be undertaken as soon as possible to determine the effective but safe dose. If the evidence continues to support the current balance of risk and benefit, the public should be educated about a personal health strategy. Information should be targeted at key groups of people, patients who might benefit from aspirin and health professionals. It is essential not to go over people's heads. This information should be precise and categorical about the benefits and risks such as adverse effects.

Is aspirin a low-cost lifesaver, Mr Spencer asked? If it is, it will have substantial impact on health at a low cost compared with current spending on cancer prevention and treatment, and its associated social and economic costs. It is clearly a long-term strategy, he said, and not without risk. europacolon, as the voice of the patient, wants to make a start now on collating the evidence and presenting it to the public and health professionals on a massive scale. If this does not happen, confusion and uncertainty will persist.

Discussion

S Lyness, S Porch, M Longley, J Armitage and J Cuzick

Ms Sarah Lyness, Executive Director of Policy and Information, Cancer Research UK, described a survey in which members of the public were asked their views about taking a daily tablet to reduce cancer risk. They were open to the idea, she said, and were incredulous when they were told the tablet concerned was aspirin. They asked why these benefits were only becoming known now and they wanted to see evidence to substantiate the claimed benefit. People were more comfortable if aspirin use was supported by a strong endorser such as the Department of Health, Bayer, NICE and particularly Cancer Research UK. Most respondents were familiar with the adverse effects of aspirin and were concerned about them. Many said they would ask their doctor for information rather than a community pharmacist. GPs, on the other hand, are unfamiliar with the evidence for reducing cancer risk and want endorsement from NICE before supporting aspirin use.

Ms Sarah Porch, Director of Services at Bowel Cancer UK, agreed that people want the reassurance of an authoritative endorsement. She said that Bowel Cancer UK is aware of the confusion about aspirin from monitoring social media – the public didn't understand the CAPP2 study, for example. There should be a single clear message from all organisations and it should be emphasised that a daily aspirin is not a substitute for a healthy lifestyle.

Professor Marcus Longley, Director, Welsh Institute for Health and Social Care, and Professor of Applied Health Policy, University of Glamorgan, pointed out that a healthy lifestyle carries no risk whereas aspirin can rarely cause stroke. Professor Cuzick said that the problems associated with aspirin occur early but its benefits come late. The public's attention span is short and the message will have to be continually reinforced to encourage long term adherence.

Ms Porch said the public are used to making judgements about risk and benefit but they need clear information about the level of risk with aspirin. Professor Jane Armitage, Professor of Clinical Trials and Epidemiology at Oxford's Clinical Trials Surveillance Unit, said the evidence is overwhelming for aspirin as secondary prevention of cardiovascular events but there is a lack of consensus about its role in cancer prevention. Professor Cuzick replied that there is a great deal of evidence but it needs to be synthesised and debated.

Where do the tablets go? Visualisation of the site of release and dispersion in the GI tract

A Perkins

Tablets are the dose form everyone prefers but swallowing them is, for many patients, an unrecognised problem, said Professor Alan Perkins, Professor of Radiological and Imaging Sciences, University of Nottingham Queen's Medical Centre.

It is known that children and some patient groups (eg, those with stroke, heart failure or diabetes, and frail elderly people) have difficulty swallowing tablets but a US study found that 40 per cent of adults had difficulty swallowing tablets and the problem was more common among women and men [1].

The way a dose form is taken has a strong influence on its transit time from the mouth to the stomach – shorter when sitting upright and if the dose is swallowed with water – and may influence its therapeutic effect. For example, the rate of onset of effect of aspirin is more rapid if a tablet is chewed than if it is swallowed in solution or as a whole tablet [2]. In healthy volunteers, the mean time to 50 per cent inhibition of thromboxane synthesis was 5.0 minutes after chewing, 7.6 minutes after the solution and 12.0 minutes after a solid tablet (Figure 1[2]). Surprisingly, morbidities which affect posture, such as kyphosis, do not appear to affect transit time.

Tablet shape and coating are also important. Transit time is shorter for oblong tablets than round ones, and for film-coated tablets compared with uncoated tablets [3]. Drug dispersion, and therefore absorption, is influenced by the disintegration characteristics of a tablet after administration. Generic tablets from different manufacturers may have different disintegration characteristics from the original brand and from one another.

Imaging studies have shown that a dose unit can remain lodged in the oesophagus for 60 minutes after ingestion but the individual may be unaware of this (Figure 2). Incomplete swallowing leading to an increased local concentration of drug can cause significant mucosal damage, most frequently affecting the lower oesophagus [4,5]. This is a significant risk for patients taking a bisphosphonate because these drugs have been associated with severe oesophageal reactions. Other drugs associated with erosive oesophageal reactions include some antibiotics (doxycycline, clindamycin, trimethoprim), NSAIDs, ferrous sulphate, theophylline and zidovudine.

Professor Perkins described a study using γ scintigraphy to quantify the oesophageal transit times of a film-coated tablet and gelatin capsule formulation of the bisphosphonate etidronate in 25 healthy volunteers. This technique is superior to a barium swallow, which is unphysiological, and to MRI because this poses practical difficulties in positioning the patient. Using a radio-labelled tablet, he showed that the transit time from the mouth to the stomach was significantly longer for the capsule (mean 24 seconds) than the tablet (mean 3.3 seconds [6]).

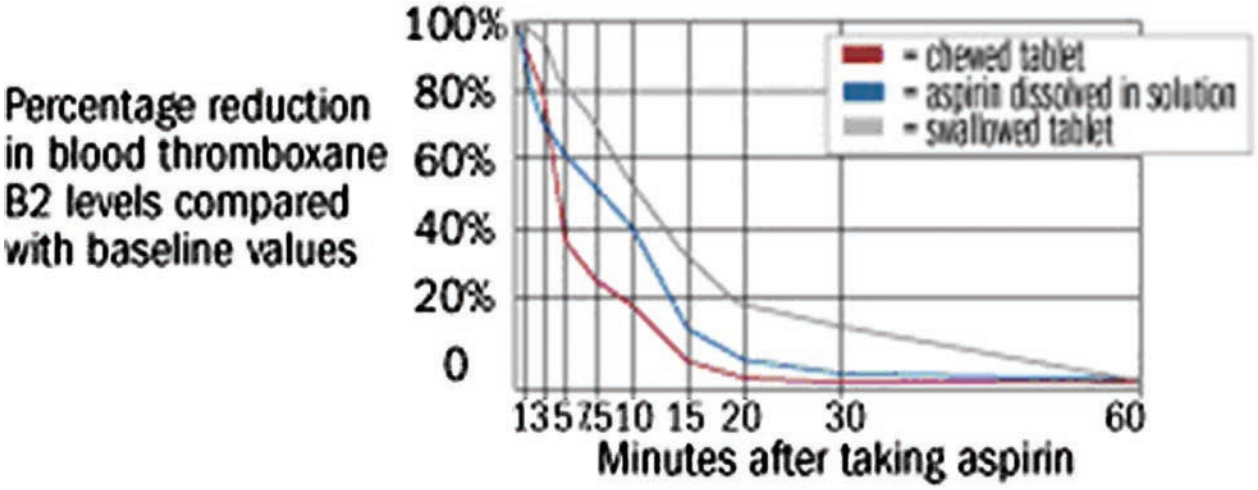

Figure 1 Time to 50% inhibition of thromboxane synthesis after ingestion of aspirin by chewing a tablet, swallowing a solution or swallowing a whole tablet [2].

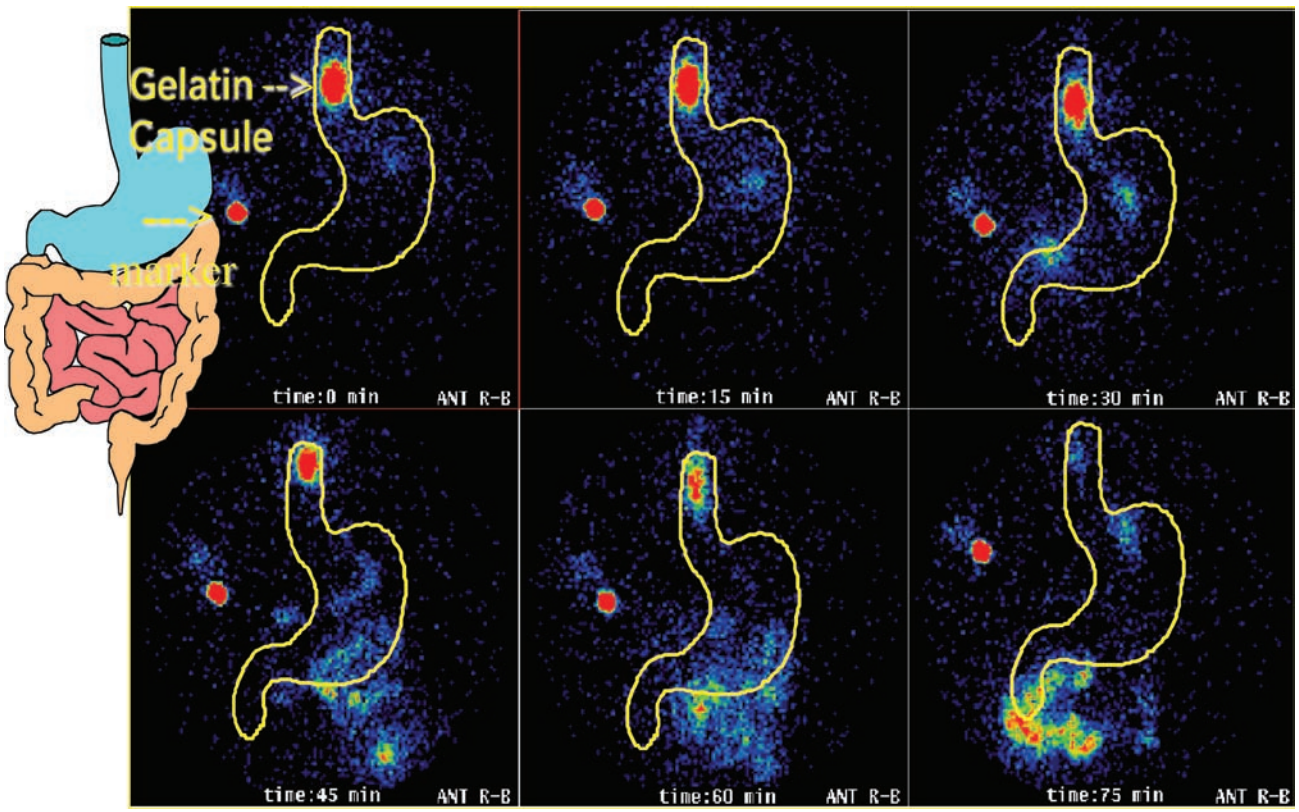

Figure 2 γ scintigraphy showing gelatin capsule lodged in the lower oesophagus for 60 minutes after ingestion.

The formulation can be manipulated to target tablet disintegration and drug release at specific sites in the gastrointestinal tract to reduce the risk of gastrointestinal bleeding – for example by enteric coating or pH-controlled release. γ scintigraphy can be used to provide visual confirmation of the site at which the drug is released and this can be correlated with blood levels.

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Aspirin – risks and benefits

P Elwood

Three authoritative reports have now identified personal responsibility as the key to achieving good health within current resources:

- The Wanless report Securing good health for the whole population stated '...health services in the UK are unsustainable in their current form unless members of the public are 'fully engaged' and take responsibility for their own health [1]'
- The Department of Health stressed the importance and potential of healthy living:'...the major aim is to 'empower' the 'millions of individuals… to make the right choice' as a means to reduce the strain on public services [2]
- The King's Fund concluded that 'the NHS should provide information, advice and support 'to enable everyone to prevent illness and lead healthier lives [3]'

Professor Elwood said there is no disagreement about the value of aspirin as secondary prevention of cardiovascular events but there is a debate about its role in healthy elderly people, in whom the balance of risk (bleeding events) and benefits (fewer cardiovascular events) may be less favourable. Weighing the pros and cons is not straightforward. It may not always be possible to recognise cardiovascular disease when its first manifestation is a fatal event; and a reduced risk of cancer should be added to the benefits side of the equation. Bleeding events are not all the same. Aspirin increases the risk of gastric bleeding by about 60 per cent – equivalent to 2–3 cases per 1,000 users – but Professor Elwood challenged the assumption that they should all be classed serious events: a haemorrhagic stroke is much more serious than a gastric bleeding event and is much rarer (about 2–3 per 10,000).

In six primary prevention trials (albeit not including very elderly people), aspirin was associated with an excess of bleeding events but mortality was similar to that among people taking placebo [4,5]. In these studies, the incidence of bleeding events was 2.2/1,000/year among aspirin users and 1.3/1,000/year among those assigned to placebo. The case fatality of those with bleeding events was 1.8 and

3.1 per cent respectively. The incidence of deaths from bleeding events was 0.040/1,000/year with aspirin and 0.049/1,000/year with placebo [4].

Any spontaneous bleeding event that occurs in someone taking aspirin will be blamed on the drug, Professor Elwood commented. Such misattribution influences the views of GPs, who are very risk averse in their prescribing. Individuals should be given relevant information and allowed to decide for themselves whether the balance of risk and benefit was favourable, he said.

It is unfortunate that no steps were taken in the large aspirin trials to evaluate ways to reduce bleeding risk. Simple measures could reduce the risk, such as taking aspirin at night (the greatest reduction in myocardial infarction risk occurs in the morning [6], gastric repair proteins are highest at night [7,8]), eradication of *H pylori* [9], treatment with a proton pump inhibitor [10,11], and taking aspirin with a source of calcium [12,13] (such as a glass of milk).

People contemplating taking low-dose aspirin should be given information about the risks. This includes the importance of checking blood pressure due to the small increased risk of a haemorrhagic stroke (increased by about 60 per cent, or 2–3/10,000/year). There is evidence of a rebound 3-fold increase in the risk of vascular events after stopping aspirin [14–16]. Even after a gastric bleeding event, the possibility of continuing aspirin with additional treatment with a proton pump inhibitor should be considered: in one small study in patients with peptic ulcer bleeding during use of low-dose aspirin (n=156), 30-day mortality due to cardiovascular, cerebrovascular, or gastrointestinal complications was greater in those who stopped aspirin than those who continued it in combination with pantoprazole (10.3 vs 1.3 per cent) despite a higher frequency of continued peptic ulcer bleeding (10.3 vs 5.4 per cent [17]).

During the discussion, Professor Elwood agreed that age influences the degree of autonomy people want in their decision-making. Older people tend to believe that the doctor knows best whereas younger adults are prepared to be more challenging. The advice of a health professional will also remain important for people who have difficulty understanding the evidence, especially those with disabilities or who are living in disadvantaged communities.

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Aspirin prophylaxis and public health

M Longley

There are three myths about the role that the public can play in determining their health, said Professor Marcus Longley, Director, Welsh Institute for Health and Social Care, and Professor of Applied Health Policy, University of Glamorgan: they cannot weigh risks and benefits; scientific uncertainty is dangerous for lay people; and most people would simply rather not know.

As with all myths there is an element of truth in these statements but modern thinking about public health is more nuanced. An independent report based on the latest evidence from behavioural economics and psychology concluded that 'People do not smoke or drink too much because they are ignorant, stupid or perverse – rather, it is the combination of the enjoyment that they get from these things and wider social or other environmental factors that mean they find it hard to adopt healthier behaviours [1]'. People gain something from unhealthy behaviours and they make an implicit trade-off of risks and benefits in choosing to continue them. Government needs to take this into account when forming its public health messages, a second report found, and it should place greater weight on informed choice and individual capacity [2].

The goal of public health policy has long been to increase life expectancy but this has been pursued at the cost of quality of life in later years [3]. Recent years have shown that preaching to people does not persuade them to change their lifestyle, so why not take a medicine