

DRUG *of* CHOICE

A daily aspirin tablet can lower the risks of many diseases – including colorectal and breast cancer – but your age is critical to avoid bleeding in the brain. Should you be taking it? **by NICKY PELLEGRINO**

When he turned 55, Professor Harvey White started taking a daily dose of aspirin to lower his risk of stroke, heart attack and bowel cancer. White is one of our most prominent

cardiologists, so if he's popping a pill in middle age as a precaution, then you'd assume the rest of us should follow suit.

After all, our rates of bowel cancer are among the highest in the world, stroke is our third-largest killer and a major cause of disability, and our heart disease rate is above the OECD average. Plus the blood-thinning benefits of aspirin may extend to preventing or slowing the spread of other cancers and potentially staving off diseases of the elderly, such as macular degeneration and dementia.

So what's not to like? Unfortunately, quite a lot. After numerous studies, aspirin remains

as controversial as it is simple and cheap.

The drug has been available as a painkilling medication for more than 100 years, but medicinal use of its active ingredient salicin, made from willow bark, stretches back into antiquity. In the 1970s, studies began to show it could prevent a further heart attack or stroke in people who had

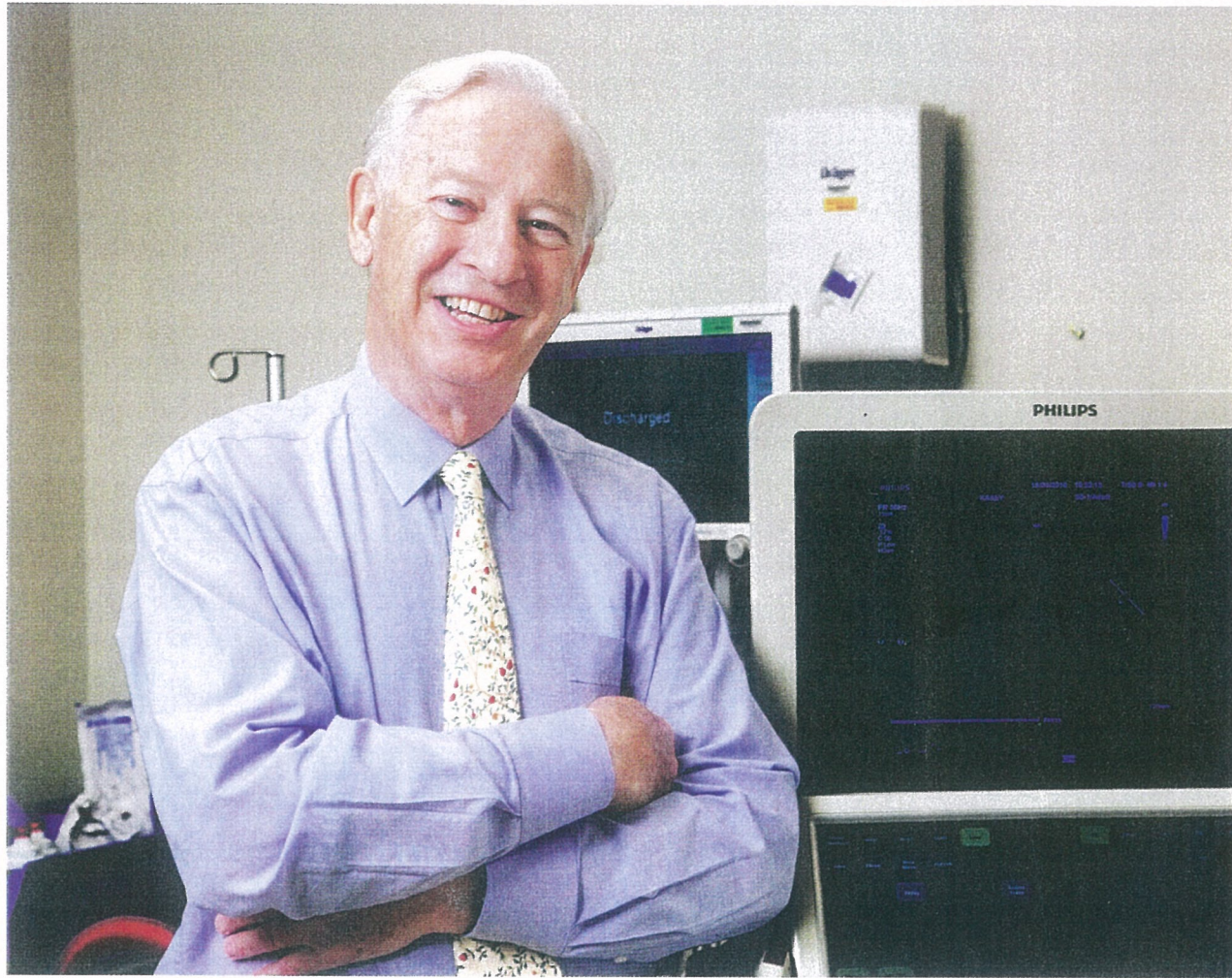
already had one. Then, in the 1980s, the Physicians' Health Study, a large trial involving male doctors over the age of 40, was halted several years early because the benefits seemed so obvious. It found that aspirin decreased the risk of a first heart attack by 44%.

After that, low-dose aspirin became an important tool in primary prevention, and today one in five American adults takes it daily to prevent their blood cells clumping together to form a clot. White says we don't have any data for the number of New Zealanders taking aspirin, but he reckons it's about half the US rate.

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Professor Harvey White: "If you're younger, then there is less benefit as your stroke risk is lower."

The trouble is blood-thinning drugs carry a risk of bleeding. So yes, they reduce the chance of clots, but they increase the chance of a stroke caused by bleeding in the brain. And since aspirin can erode the stomach lining, there is more chance of bleeding in the gut as well.

The elderly have the most to gain and also the most to lose. The older you are, the higher your risk of a stroke or heart attack but also the higher the risk of a serious bleed. In fact, a recent study from the University of Oxford suggests that daily low-dose aspirin may be causing more than 3000 deaths a year in the UK and found those over the age of 75 were 10 times as likely to suffer a bleed as those not taking the drug.

A NUMBERS GAME

White, director of coronary care and cardiovascular research at Auckland City Hospital, remains convinced that swallowing a daily 75-100mg of the drug is a sensible idea. For him, it's a numbers game. He has looked

at the available evidence and seen that for a man or woman in his age group, there is still considerably more chance of benefits than there is of a bleed.

"If you're 50 to 59, you should take low-dose aspirin as a preventative," he says. "If you're younger, then there is less benefit as

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– Professor Harvey White

your stroke risk is lower. And if you're older, there is more chance of bleeding. So it's a continuum of balancing the risks."

White refers to guidelines released last year by the US Preventive Services Task Force following a review of numerous studies. These say that if you're healthy, without any of the risk factors for bleeding – smoking,

high blood pressure, previous bleed, diabetes – and you're under 70, the benefits of daily low-dose aspirin weigh the harms, and the recommendation is to consider taking it if you have or greater risk of cardiovascular and colorectal cancer.

For women, there seems to be a particularly strong stroke benefit. And significant cancer prevention, people are advised to take aspirin for five to 10 years, usually they will begin between the ages of 50 and 59.

Once you're over 70, it becomes difficult to determine whether the potential benefits are outweighed by the potential harm. "We were operating in the dark when we prescribed aspirin to older people," says Professor John McNeil, head of Monash University's Department of Epidemiology and Preventive Medicine in Melbourne. "The evidence around to tell us whether it was good for primary prevention in the seventies. It became obvious we needed a clinical trial to see whether we should be prescribing it."

KEN DOWDIE

Professor John McNeil: "We were operating in the dark giving aspirin to older people."

That trial is called Aspre (Aspirin in Reducing Events in the Elderly), the largest primary prevention study ever undertaken in healthy older people. Its scope extends far beyond aspirin's effect on the risk of cardiovascular events, with sub-studies looking at whether its anti-inflammatory action could stave off depression, hearing loss, bone fragility and severe infection in older people, and whether it might help in the early stages

Blood-thinning drugs reduce the chance of clots, but they increase the chance of a stroke caused by bleeding in the brain.

of age-related macular degeneration and slow down cognitive decline.

Eventually, there were 19,000 people aged 70 or more, mostly from Australia and the rest from the US, taking a daily 100mg aspirin or a placebo and being measured in various ways.

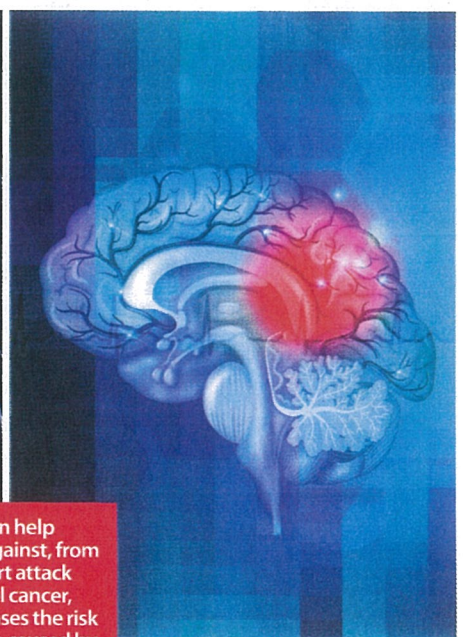
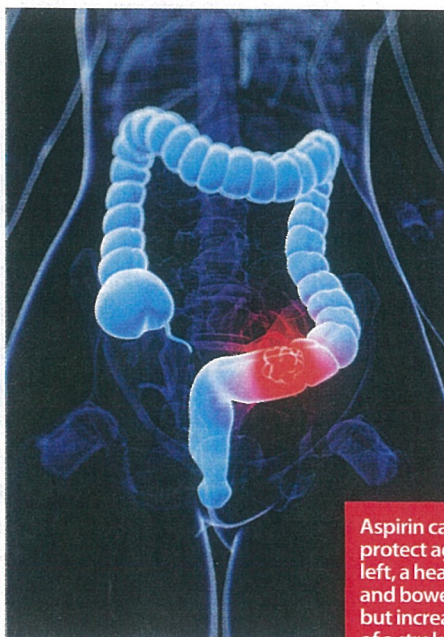
Then in June, the funding body, the US National Institute on Aging, which had been monitoring the data being collected, pulled the plug on the intervention side of the study. The Aspre participants were advised to wean themselves off their medication earlier than intended, not due to new evidence



of bleeding risk but because aspirin wasn't showing any clear benefits for the study's main aim: to extend disability-free survival.

"It's disappointing, but the question had

to be answered one way or another, because a hell of a lot of people are taking aspirin," says McNeil, one of the lead Aspre investigators. "And we're still collecting and



Aspirin can help protect against, from left, a heart attack and bowel cancer, but increases the risk of a stroke caused by bleeding in the brain.

GETTY IMAGES



GUY FREDERICK

Mark Corbitt: "A lot of people don't want to change. They'd rather pop a pill."

analysing the data. We might see big benefits for some people and risks for others.

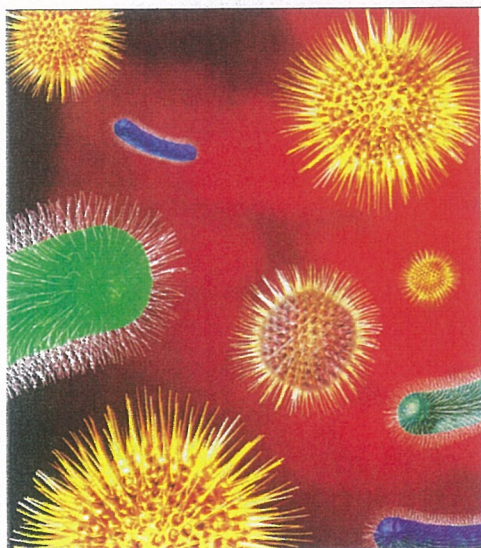
The results are due to be published in 2018, but the cancer angle will require participants to be followed for several more years. In the meantime, there isn't enough data from Aspree to present a compelling case for the healthy elderly taking aspirin as a preventative.

For others, some persuasive evidence exists out there. A 2015 study at Leiden University in the Netherlands found that patients with gastrointestinal tumours who took aspirin as part of their cancer treatment doubled their chances of survival. One theory explains this down to aspirin's antiplatelet effect.

Gastrointestinal-tumour patients who took aspirin as part of their cancer treatment doubled their chances of survival.

platelets, which try to stop bleeding, to clump around tumour cells, making it harder for the immune system to recognize them and prevent them from spreading. Aspirin inhibits this, allowing the immune system to detect the cells and eliminate them.

The strongest connection is for colorectal cancer – studies have shown it lowers the risk of dying from it by about 30% for men and women. New research using data from the California Teachers Study has shown



Gut feeling about aspirin

Some of the effects of aspirin may result from changes to the gut microbiome. Gut microbes reflect what we eat, and that includes over-the-counter aspirin.

Studies have shown it's possible to identify regular aspirin users from the levels of certain bacteria in their gut. Aspirin users have more of four particular species, but scientists don't yet know whether the changes reflect the use of aspirin or the underlying condition the aspirin is being used to treat.

In the US, a University of Minnesota study is investigating whether aspirin reduces the risk of bowel cancer by targeting the gut microbiome.

The clinical trial, due to be completed in August, is examining the correlation between aspirin-related changes to the microbiome and levels of inflammatory biomarkers in blood and urine.

that regular use of low-dose aspirin also reduces the risk of breast cancer in women by 16%. This may be down to its anti-inflammatory action; but it is also a mild aromatase inhibitor, reducing the amount of oestrogen in the body.

Another large clinical trial called Add-Aspirin is being done in the UK and India to find out whether taking daily aspirin for five years after treatment for a variety of early-stage cancers can stop the disease or delay its return. So aspirin may still turn out to be a cancer hero.

ASPIRIN AND STROKES

It has been established that if you've already had a heart attack or stroke, then taking aspirin will substantially reduce the risk of

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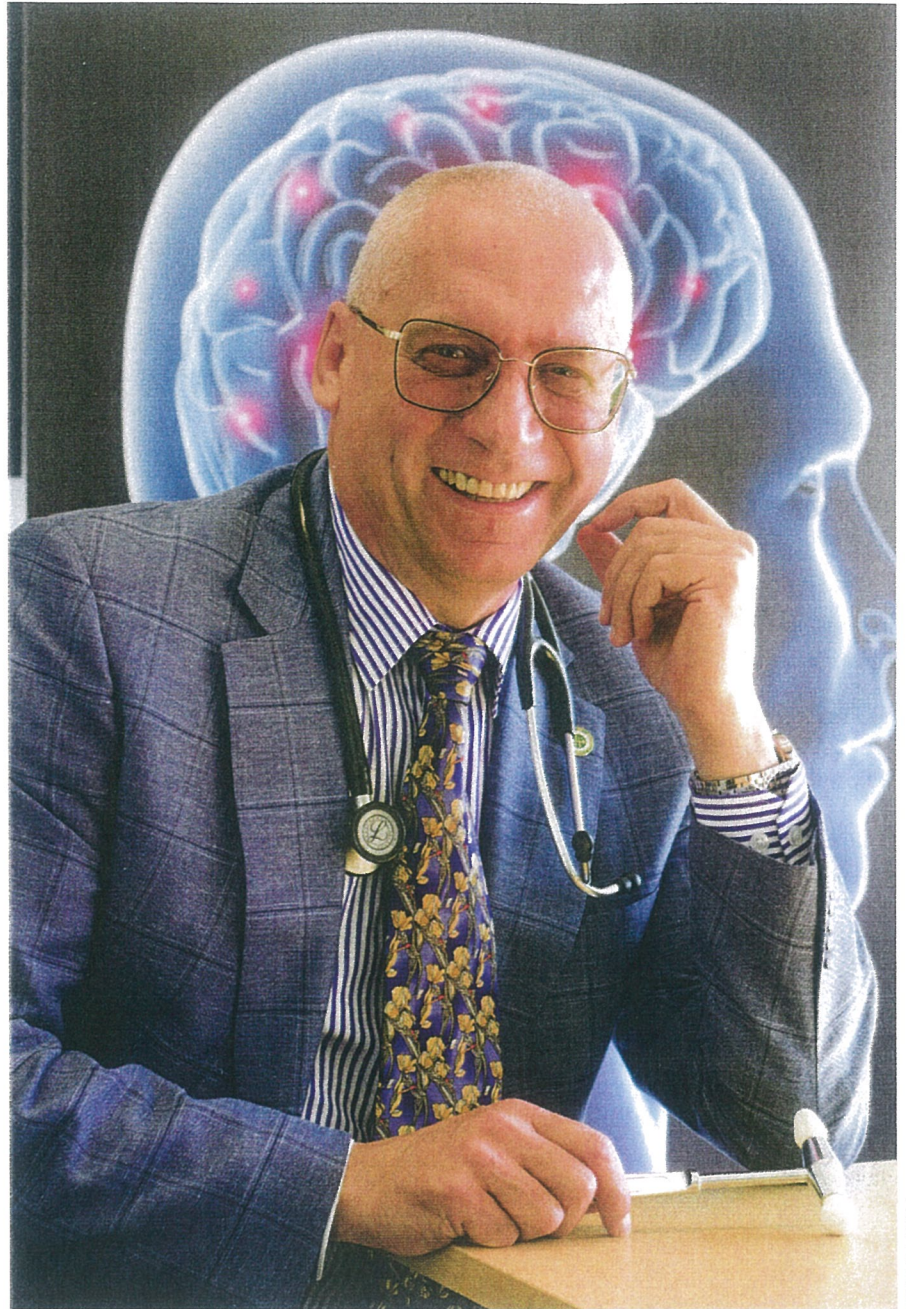
suffering a second one and it is commonly prescribed. There is also an argument for taking the drug if your risk of a stroke is high.

However, when he had a series of strokes while mid-air on a flight from Sydney to Wellington, Mark Corbitt was very much low risk. He was 50, didn't smoke or have high blood pressure and had an only slightly elevated cholesterol level.

"It pretty much came out of the blue," he says. "Two months earlier, I'd done a 100km bike race and I was having a complete medical every two years. So I considered myself very fit and healthy."

Corbitt had blacked out a couple of weeks earlier, but he'd put that down to tiredness as he'd been working hard in his then role as chief information officer for Contact Energy. Then on the plane, when he lost control of one side of his body and his speech became slurred, he realised what was happening and alerted the flight attendant. Half an hour later, he had a bigger stroke. "That one locked me into my seat for the remainder of the flight."

In Wellington Hospital, the strokes kept coming, and after having a CT scan, Corbitt learnt he had a blocked artery in his brain



TONY NYBERG

Professor Valery Feigin: it's not only your absolute risk of stroke that you need to be aware of.

stem. Fortunately, his treatment was successful, and two years later, he's back to full health. He takes a combination of statins and aspirin to prevent the same thing happening again, but his neurologist told him that to maximise his chances of staying stroke-free, he also needed to revamp his diet.

"I ate a lot of meat and dairy," admits Corbitt. "It was a standing joke in the family that if they cooked a vegetarian meal, they'd have to do a sausage for me. I haven't had any since I left hospital. Now I eat a plant-based wholefood diet plus some fish."

It took him three months to adjust to

the change. "But if someone throws you a lifeline, you don't question whether you should take it."

Family, friends and workmates were all affected by his experience, because they had considered him to be the healthy one. "Suddenly no one was touching the chocolate afghans in meetings any more."

Now Dunedin-based, Corbitt isn't tempted to go back to his old high-fat diet, even though at times it can be difficult to find healthy food.

"I want to stay mobile to my late seventies like my parents. While you can't

To take or not to take

New research is helping balance the risks and harms of aspirin. **by DONNA CHISHOLM**

Working out who should be prescribed aspirin to prevent heart attacks and stroke and who should not is the subject of a three-year, \$600,000 research effort at the University of Auckland.

Public health physician Vanessa Selak is leading efforts to develop a risk-benefit chart that will enable doctors to readily measure when the adverse effects of aspirin – gastrointestinal or brain bleeds – outweigh its anti-clotting benefits.

People who've already had a heart attack or stroke are usually prescribed aspirin in conjunction with other drugs, including medicines to reduce blood pressure and cholesterol.

But the advice is less clear-cut for those who haven't had a cardiovascular event but are nonetheless at high risk.

In New Zealand, aspirin isn't generally recommended for people whose

Public health physician Vanessa Selak hopes her work will become a Predict program add-on.

five-year risk of a heart attack or stroke is estimated at less than 20% – a much higher threshold than in the United States, where advice suggests it's useful when the 10-year risk is as low as 10% (roughly equivalent to a five-year risk of 5%).

It's a group for whom the balance of benefits and harms is most uncertain, says

Selak. "The assumption that you should be starting a medication when your risk a cardiovascular event is above a certain threshold is based on the assumption that the benefits will outweigh the harms – and that the harms stay about the same irrespective of cardiovascular risk.

"But it's more subtle and more complex than that.

Aspirin isn't generally recommended for people whose five-year risk of a heart attack or stroke is estimated at less than 20% – a much higher threshold than in the US



"It's hard to make that statement without understanding what the risk a bleed is, and that's a fundamental piece of information that's missing, because it underpins everything."

The main risk factor for

live in fear, you have to do what you can. Unfortunately, a lot of people don't want to change. They'd rather pop a pill."

LIFESTYLE VS DRUGS

Auckland's Professor Valery Feigin would agree with him. The director of AUT's National Institute for Stroke and Applied Neurosciences is passionate about prevention and believes the emphasis should be on lifestyle rather than drugs.

"Lifestyle risk factors are responsible for three-quarters of the burden of stroke," he says.

"And in New Zealand the prevalence of risk factors is very high: obesity, high blood pressure, our smoking, which is still high in comparison with Australia, and our

blood-glucose levels, which are the highest in the world – that's a shocking fact. We all know it causes diabetes, which is related to stroke and cardiovascular disease."

The New Zealand health system is already

"Lifestyle risk factors are responsible for three-quarters of the burden of stroke."

struggling to adequately rehabilitate stroke survivors. Feigin believes that as our population ages and the number of survivors increases, this will threaten the sustainability of the system. And, he points out, we

are seeing increasing incidences of stroke in young people.

By now, everybody knows the key to better health is to be active, eat well and avoid smoking. We've all been well educated in how it reduces our chances of developing a range of non-communicable diseases including stroke, heart attack and cancer. But how many of us are following the recommendations?

"The key is motivation," says Feigin. "It involves telling people the truth about their individual risk. The best way to do this is mobile technology. It's so widely used that it would be stupid not to use this opportunity to provide health information."

Feigin's belief is that it's not only about the absolute risk you need to be aware of

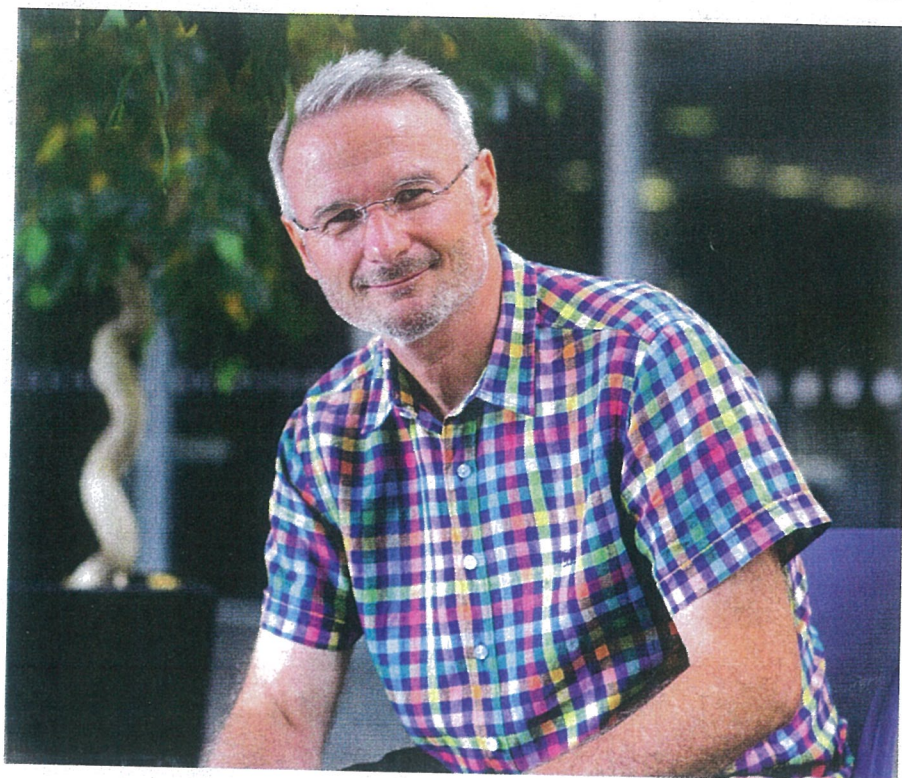
an aspirin-related bleed is older age, but gender also comes into play, with men at higher risk than women. Diabetes, hypertension and smoking – all things that increase the risk of cardiovascular disease – also increase the risk of a bleed. The question is by how much.

“Balancing up the risks and harms is quite an art form,” says Selak. “What I’m trying to do is help doctors to unpack that in a more objective way.”

Selak’s Health Research Council-funded work uses data gathered by Auckland professor of epidemiology Rod Jackson over the past 15 years from more than 500,000 New Zealand patients who’ve had cardiovascular risk assessments through their GPs. By tracking their outcomes, he has produced the Predict computer algorithm for New Zealand patients, which advises doctors about when to start treating patients and with what. It calculates an individual patient’s risk of heart attack or stroke based on factors including age, blood pressure, cholesterol level, smoking and diabetes.

Now Selak hopes her work, assessing the risk of treating with aspirin, will become an add-on to the Predict program. She says it could be available in general practice as early as the end of 2018.

In people aged 60-69 without diabetes and without a history of cardiovascular disease, the rates of major bleeds in those not on aspirin are 4.61 per 1000 person years in men and 3.45 in women. But if they receive aspirin, the expected rate of



Professor Rod Jackson has developed the Predict program, which advises doctors on when and how to treat individual patients.

major bleeds rises to 7.10 in men and 5.31 in women.

The algorithms doctors currently use to guide patients on what treatment to have and when to start it – which are soon to be replaced by Jackson’s – were based on heart disease risk scores from patients in the long-running Framingham study in the US.

But Jackson has found those scores

overestimate actual risk by nearly 100% when compared with the New Zealand cohort. That’s largely because the Framingham study started in 1948, but coronary death rates have been plummeting since the late 1960s.

Jackson says this negates the effect of the differences in the percentage thresholds being used in the US and New Zealand to begin treatment.

STEPHEN ROBINSON

your risk in comparison with healthy people your age. To that end, AUT has developed a free app, Stroke Riskometer, which to date has had more than 100,000 downloads worldwide and comes up in the No 1 spot if you search for stroke in the Apple App Store.

It takes a few minutes, covers 18 risk factors, including gender, ethnicity, family history, fruit and vegetable consumption, traumatic brain injury and medical history.

And Feigin is right. Learning that my absolute risk is 0.72% didn’t worry me, but discovering that this is twice what’s normal for my age prompted me to use the app to look further into what I’m doing wrong.

AUT has studied a group in South Auckland using the app and found it helped a significant number of them to make

behavioural changes. It’s self-management,” says Feigin, “although ideally it would be combined with a doctor’s advice, because the app is not perfectly individualised.”

He is pleased that in the latest Interna-

AUT has developed a free app, Stroke Riskometer, which covers 18 risk factors.

tional Classification of Diseases, stroke has been listed under neurological disorders rather than cardiovascular. He was part of the World Health Organization group that advised on that change and sees it as a major

shift that will have positive results both for stroke services and research.

“Stroke research has lagged so far behind. Previously, it was not a priority. Now it’s in its proper place, hopefully it will attract more funding.”

In the meantime, a daily low-dose aspirin may be worth considering for primary prevention if you’re under 70.

For those who are older, heartburn drugs known as proton-pump inhibitors can be prescribed to lower the chance of a bleed, although these carry their own side effects and hazards.

In Feigin’s opinion, medication shouldn’t be our first or only line of defence. “Aspirin is not improving your lifestyle. It’s not a magic pill.” ■