Chest pain during exercise – or how to avoid getting stented

(pages 47-54 in Gøtzsche PC. Survival in an overmedicated world: Find the evidence yourself Copenhagen: People's Press; 2019).

A lawyer in New York developed chest pain when exercising and consulted his internist, who ordered a stress test with an echocardiogram (heart ultrasound).[10] No abnormalities were found but his distress came later when he saw that the hospital had charged some $8,000 for this test. Despite having excellent insurance, he was asked to pay $2,000 of the total. He refused when he found out that other hospitals charged between $1,200 and $6,000 for the same test and, after a lengthy exchange, the hospital dropped its demand.

Americans are proud of their freedom, but they also have the freedom to exploit the suffering of their neighbours as much as they wish. Greed to the extreme reigns. Half the people in the world earn less than $4,000 a year.

It should be noted that many doctors do these procedures because they believe them to be helpful, so the crucial question is whether the test was necessary? All doctors know chest pain may develop during exercise; we call it *angina pectoris*, or just angina, which means chest pain. Angina is caused by a reduced blood flow to the heart muscle, which is almost always secondary to arteriosclerosis of the coronary arteries. Although the lawyer's tests were normal, angina was probably the issue and drugs can alleviate the symptoms. Most people have heard of nitroglycerin, an ingredient in dynamite also used to treat angina. Today guidelines recommend a beta blocker or a calcium channel blocker as first-line treatment. You will find this information if you google *angina treatment* and look up the NICE guidelines (National Institute for Health and Care Excellence in the UK).

Another test for people with chest pain is coronary angiography. A catheter is inserted into the artery in the groin and moved toward the heart, and an X-ray of the coronary arteries is obtained by injecting contrast. I once discussed clinical cases with colleagues in the United States and they told me of a patient who got chest pain when running uphill, which led to a coronary angiography. I questioned this and asked why they did not intervene without the test. They replied that if the coronaries were too narrow, one or more stents could be inserted to widen them.

Now we have a whole range of interesting questions to examine: How good is a stress test at determining whether a patient has angina? How good is ultrasound? Is it perhaps used for other purposes?

I would argue that since we already knew the patient had angina - defined as chest pain during exercise - then why do a stress test? The patient already did his own stress test by running so why repeat this on a treadmill or stationary bicycle at the clinic? And if the test was negative, it would be a false negative, because we already knew the patient had angina.

Guidelines or websites of professional associations are often good starting points when trying to find the rationale for medical interventions. By googling *angina*, you will find a description of it on the American Heart Association website.[11] Referring to the exercise stress test, they state it can "show if the blood supply is reduced in the arteries that supply the heart." That can be seen on an electrocardiogram (ECG) taken while you do the test. On the other hand, what is the likelihood that your chest pain is caused by something else? Very small.

Next, I tried *exercise stress test cochrane*. There was a link to a Cochrane review, but the abstract tells us that the review is about screening patients with chronic kidney disease for the risk of coronary artery disease. Not what we are after.

Another link looked more relevant - a systematic review and meta-analysis of prospective studies of the accuracy of exercise stress test for coronary artery disease [CAD][12] - perfect. The authors included studies investigating "a representative sample of patients over the age of 18 years, who had symptoms suggestive of CAD (for example, chest pain or breathlessness), or who were asymptomatic but had risk factors for CAD (e.g. diabetes mellitus, hypertension)."

The Google link brought you to the methods section of the article, which is not the original, but a copy published by Medscape. If you click *Abstract and Introduction*, you will be asked to register for free at Medscape in order to read the article.

That is easy but there is a quicker way. Go back one step to the methods section where the full reference of the article is found at the top. Open a new window in your browser and go to PubMed, ncbi.nlm.nih.gov/pubmed, *PubMed Tools* and *Single Citation Matcher*. Enter a few details from the reference of the article, e.g. *Int J Clin Pract* in the *Journal* field, *2012* in the *Date* field, and *477* in the *First page* field; click on *Search*, and the abstract appears.

It is often difficult to know when to stop. Is reading the abstract enough? Abstracts can be misleading, but sometimes they are sufficient, so let us take a look at this one.

"*BACKGROUND*: Exercise stress testing offers a non-invasive, less expensive way of risk stratification prior to coronary angiography, and a negative stress test may actually avoid angiography." Looks promising so far.

Under *METHODS AND RESULTS*, the authors mention they systematically reviewed the literature to determine the diagnostic accuracy of exercise stress testing for coronary artery disease using angiography as the gold standard. That looks very good.

The authors included 34 studies with 3,352 participants, which is a very large sample for a study of diagnostic test accuracy. They reported that bicycle echo (ultrasound) testing performed better than treadmill echo testing, which outperformed both treadmill ECG and bicycle ECG. They documented this by using likelihood ratios. A positive likelihood ratio of 11 for bicycle echo testing means that people with CAD are 11 times more likely to have a positive test than people without CAD. Conversely, a negative likelihood ratio of 0.2 means that people with CAD are 5 times less likely to have a negative test than people without CAD.

The link to the full article is to the right of the PubMed abstract and access is free. What you always need to ask is: Were the patients who participated in the studies similar to the lawyer (or yourself)? You can already see in the methods section on Medscape that they were not, since some of them did not have angina symptoms, only risk factors for coronary artery disease.

There are other reasons why this good review may not give you the answers you are looking for. In their abstract, the authors conclude that exercise testing is more useful at excluding CAD than confirming it, which suggests that some patients using this test may be spared angiographies, which are more expensive. However, in the main body of the article, the authors say exactly the opposite, namely that exercise testing is probably more useful at confirming CAD than excluding angiographies. So, what is correct?

Despite these issues, I think we may come to useful conclusions by reading the paper. The authors say that only 8 of the 34 studies were blinded to the reference standard and the test. Blinding the investigators is the most important precaution we have, and when they are not blinded, there is a risk that they will report socially desirable answers rather than what they would

if blinded. Thus, the studies probably exaggerate the accuracy of the test. Even so, the seemingly impressive likelihood ratios are not so impressive when we look at more readily understandable numbers. The median prevalence of CAD in men in the studies was 62%. So, before doing the test, a man's risk of having CAD was 62%. A positive exercise test increased his risk of having CAD to 82% and a negative test decreased the risk to 37%. Moreover, our patient does not belong to a group where 62% has CAD; he belongs to a group where virtually everyone has CAD, and where a positive test result would, therefore, not add much to what we already knew.

In the discussion section, the authors describe a study of a US population that showed that 41% of the patients with a positive result on stress testing had CAD on coronary angiographies while 35% of those who did not undergo any testing had CAD. This depressing result tells us that stress testing would perform very badly if used as a screening test, e.g. at a regular health check.

The authors wrote that improved risk stratification prior to angiography is needed. Perhaps it is. But maybe their conclusion should have been that stress tests are not useful. It is very hard for clinicians to admit that their usual interventions are not really helpful. They try to avoid this unpleasant conclusion by saying that one thing or another needs to be improved. Or by saying that more research is needed - one of the most abused phrases in medical research. Very often, we do not need more research. We need clinicians who dare reach conclusions that are in accordance with what they have seen.

The crucial question is: Are there any trials that have compared outcomes for patients with angina treated without stress tests or angiographies, with patients who underwent tests before treatment? Such trials would give us the answer we are looking for.

You could search on PubMed using "*exercise stress test*" in the search field. It is important to use quotation marks. When I did this search without using quotation marks, 89,087 entries appeared and only 1,251 came up with quotation marks. Then I went to *Article types* on the left, *Customize,* checked the boxes *Randomized, Controlled Trial* and *Systematic Reviews,* undid any other checkmarks there were on the list, clicked *Show*, and clicked on *Randomized Controlled Trial* and on *Systematic Reviews* so that the checkmarks (✓) were visible.

105 titles came up which took me six minutes to browse. Most of them were dealing with drug therapy - not a single one was relevant.

As Cochrane reviews are indexed on PubMed, it is highly unlikely that anything was missed by not searching in the Cochrane Library. But for the sake of the example, I went to cochranelibrary.com, *Cochrane Reviews*, *Search CDSR*, *Browse by Topic* and found *Heart & circulation*. 57 reviews appeared in the category *Myocardial ischemia/coronary disease,* which can be browsed in less than five minutes. When the category was opened, seven reviews about angina came up - sufficient for browsing.

Another category also came up under *Heart & circulation* called *Non-specific chest pain*, which is not relevant since the lawyer had specific chest pain.

We are left without clear answers. I may be oversimplifying things - I am not a cardiologist - but after all this, I do not find further pursuit of this issue worthwhile. I am not convinced that any testing is needed for patients like our lawyer with the typical symptoms of angina. Just treat him and similar patients for angina and save up to $8,000 each time.

I shall now tell you my own story, which illustrates the diagnostic difficulties in this area and how difficult the practice of medicine can be.

In 2010 at the age of 60, I ran fairly fast in a 5 km relay. After 4 km, I got a strange and unpleasant feeling in my chest that prevented me from running. Since I had never had heart problems or any risk factors for heart disease, I was surprised that this could happen. After a short break, I resumed running but was forced to stop again because of cardiac arrhythmias and the same strange feeling.

Some days later, a colleague performed an echocardiography on me while I rested. It was normal. Yet the symptoms came back when I was running, with a regular fast pulse at about 200 or an irregular fast pulse after 1-2 km, which I handled by decreasing my pace. In doing so, I avoided any further problems for the rest of my run. Yet, some months later, it became worse. Sometimes it was so bad that I had to walk home because every attempt I made to start running brought the arrhythmias back. I never had any chest pain but that strange sensation in the chest, described above was breathlessness, which is one of the symptoms of angina.

Ultimately, I decided that I needed to be examined. Cardiac monitoring while I slept showed occasional sinus tachycardia, probably atrial fibrillation and runs of four ventricular tachycardias, which worried me somewhat. The stress test was clearly positive even when I ran on the treadmill at a rather slow pace with little effort and without symptoms. I did not know at the time how unreliable stress tests are. Given my education and my time spent on a coronary care unit as a doctor, I assumed that stress tests were quite reliable.

I was left with no doubt whatsoever that I had coronary heart disease, despite all my years enjoying various sports and my lack of risk factors. I was encouraged to take a small dose of aspirin every day but, after looking up the evidence, I refused taking it.

How can you find out whether you should accept or refuse aspirin? Please think about that before you continue reading, then do the search and see what you find. I will not give you the 'solution' until later.

Because my symptoms, the cardiac monitoring results, and the stress test all complimented each other very nicely, no one had any doubt I had coronary heart disease - one of the most common causes of death.

It took some time to get used to my new situation. I looked up various reviews and found out by how many times my risk of death had suddenly increased. You might see this a little masochistic, but I have a habit of wanting to know as much as possible about everything. I felt I stepped out of my usual, "Don't worry be happy" attitude to life and walked straight into the antechamber of death. It felt like that until I got used to my new situation.

I was put in a hospital bed next to a young man with blocked coronaries due to a hereditary condition. His father had died very young. I felt very sorry for the man and I even felt a little sorry for myself. So, these people are my new companions, right? One of the many bad things about being hospitalized is you are no longer in healthy company. Now it is all about sick people. We should spend as little time as possible at hospitals because staying there does not bolster self-confidence.

The next day I was supposed to have one or more stents inserted into my arteriosclerotic arteries. I am still surprised I said yes. It happened so quickly, I had little time to think. I already knew - contrary to what people think – that coronary bypass operations do not prolong life; they merely have a symptomatic effect. Therefore, I supposed the same was true for stents and I did not like the idea of having tubes inserted into my coronaries. Furthermore, my ailments were minor. I had no problem playing tennis. I could give up running and, instead, race around on my bike.

Why did I accept the stenting? I just do not know. I should have studied the evidence first.

There I was, lying on the table with a catheter in my groin, awaiting the inevitable. I would be leaving my wonderful world of freedom and entering the land of sickness and dependency, destined to die too soon. Life would never be the same.

Then the cardiologist said, "Turn the screen so that Peter can see his arteries." I was stunned. My coronaries were smooth - without a trace of arteriosclerosis. They might have belonged to one of my medical students.

What on earth was this? My cardiologist said I was false positive and recommended that I continued running as much as my symptoms allowed. I agreed. I asked the cardiologist who had subjected me to the stress test to explain it. He could not. We all knew that, under certain rare circumstance, people could have spasms in their arteries. I assumed that was the case for me. Since there were no arrhythmias during the positive stress test, that could not be the reason. I might never find an answer.

I still run - more than ever - sometimes 8 km every day of the week together with my wife who has run half-marathons. I am too lazy for that. When we run too fast and I get uncomfortable chest arrhythmias, I just pause for a few seconds. Life is now far better than in 2010, demonstrating that it does not always go downhill - it does improve at times.

Good doctors become increasingly humble with age because they realize that many of their patients do not correspond to what they have read in their textbooks. Conversely, poor doctors become increasingly arrogant as time passes. I was lucky enough to be looked after by good doctors.

Did you find out how to search for the effects of aspirin? Found anything helpful? It is not an easy task. Since aspirin is used for many things, we need to focus on heart disease. Is the issue about using it for therapy or prevention? I would say prevention because aspirin lowers the risk of blood clots, which is why it is recommended for people who have had heart attacks.

You could try googling *aspirin heart cochrane*. If you type *aspirin coronary cochrane*, the first two entries will be the same.

The first link goes to a Cochrane review of aspirin for primary prevention of coronary artery disease[13] - not directly relevant for my case because I believed I already had the disease. Yet what people usually want to know is how to prevent heart attacks, so perhaps this review is of interest after all. It turns out to be only a protocol for a Cochrane review. Since it is from 2004, the review should have been completed and published long ago. (Therefore, I have written the Cochrane review group listed just under the title of the review, *Editorial Group:* Cochrane Heart Group, and asked them to remove this outdated protocol from the Cochrane Library.)

Reading the background section of a review – *Introductio*n - is often useful because it tells you how people think about the issues and provides references that might answer your question. The protocol says that two meta-analyses demonstrated that aspirin used for primary prevention significantly reduced all cardiovascular events by 13-15%, and myocardial infarction (heart attacks) by 30-32%. But it also says that aspirin can have serious adverse effects, e.g. gastrointestinal bleeding and haemorrhagic stroke. Therefore, guidelines only recommend aspirin for men at high risk. I was not a high-risk man.

The next Google entry was a review that compared aspirin to aspirin in combination with another drug for preventing cardiovascular disease.[14] This is not relevant because we want to

know the effects of aspirin versus placebo. On the other hand, it takes only a few minutes to read the background section. It says that a meta-analysis has shown that the relative risk reduction of death, myocardial infarction and stroke in patients at risk of cardiovascular events is approximately 20%, and that protection with antiplatelet therapy - e.g. aspirin - for patients at high risk of cardiovascular disease remains unsatisfactory in absolute terms.

Although I was at risk of cardiovascular events, I felt that the risk was not great. If I had been taking aspirin and I fell off my bike or stumbled on a root and hit my head while running in the forest, it would not be pleasant because aspirin might cause a brain haemorrhage.

Other people might have reached other conclusions than I, but this example illustrates the importance of not treating everyone the same way - which guidelines tend to do.

One of the most important of all questions is this: "Am I similar to the patients in this review?" In the entire world, is there not a single, large trial comparing aspirin to placebo in patients like me? Not a trial comparing patients who never had angina (primary prevention) and not patients who had previous heart attacks or other serious events - something in between.

If you search on *aspirin angina* in PubMed, it corrects into *aspirin AND angina* (2,273 entries). Limit your search to *Clinical Trials* or *Systematic Reviews*: 631 entries. Still a bit too many but they could be browsed through in a day. For *Systematic Reviews* alone (check the *Clinical Trials* box to make it disappear) – you get 122 entries. At the top, sort by clicking *Most Recent*. The first entries are about all kinds of irrelevant issues such as patients with diabetes. We can narrow the search to include only entries with angina in the title: *aspirin AND angina[ti].* PubMed has several such useful features. Now you are down to 24 links, most about unstable angina. If you wish to eliminate these, you can search for *aspirin AND angina[ti] NOT "unstable angina"*, and you are left with three documents - two narrative reviews and one guideline - none of which are relevant.

Did I have stable or unstable angina? Googling *stable angina* provides the answer. The first link went to the American Heart Association website. Stable angina was what I had. Pain or discomfort occurred when my heart worked harder - it did not come by surprise, episodes of pain tended to be similar, usually brief (5 minutes or less) and relief was attained through rest or medication. You might experience it while running and normally this type of chest discomfort is relieved through rest, nitroglycerin or both.

I wondered why the cardiologists wanted to insert stents in me when my problem was so banal and easy to live with. It did not make sense to me - if I had done my homework, I would have refused it.

One question remains. Do stents improve survival? I did a basic search of the Cochrane Library for *stent*. Stents are used in many places in the body, e.g. even in the biliary duct, but the 58 titles that came up were quickly browsed. One study compared two types of stents. I read the background section:[15] adverse events associated with percutaneous coronary intervention include death, coronary artery complications, e.g. perforation of the artery, distal embolization (passage of an intravascular mass capable of clogging capillaries), or stent thrombosis, myocardial infarction, bleeding or infection of the access site, bleeding in the abdomen, stroke, and acute kidney failure. Holy smoke! I had exposed myself to all those risks for no good reason.

Do stents improve survival in those who need them? That is difficult to find out, because the many trials that have been performed compare stents with something else, like bypass or balloon angioplasty, not with doing nothing. How do you search on doing nothing? That is really difficult. I decided to cut this Gordian Knot which, to me, always means Google: *do stents improve mortality*.

It worked. A paper in New York Times described what we need to know with reference to a recent meta-analysis.[16]

The researchers reviewed eight randomized trials (7,229 patients) comparing percutaneous coronary intervention (PCI) with standard medical care. Aha, there it was. Remember that. Try the phrase *standard medical care* or *standard care* on Google when you do not know what to do about studies without placebos.

Three trials enlisted stable patients after myocardial infarction, and five trials enlisted patients with stable angina and/or ischaemia on stress testing.[17] Interesting. I finally found patients like me.

"Prescribing beta blockers, ACE inhibitors, statins and daily aspirin — now standard for treatment of stable coronary artery disease — was just as effective as stent implantation for prevention of chest pain, heart attack, the need for a future PCI and death."[16]

One of the authors of the meta-analysis said that more than half patients with stable coronary artery disease are implanted with stents without even trying drug treatment. They believed the reason was financial.[17] "In many hospitals, the cardiac service line generates 40% percent of the total hospital revenue, so there's incredible pressure to do more procedures ... When you put in a stent, everyone is happy — the hospital is making more money, the doctor is making more money — everybody is happier except the health care system as a whole, which is paying more money for no better results."

The cost of the procedure varies from about $30,000 to $50,000, and more than one million are performed every year in the United States. That makes a total of around $40 billion a year for doing something unnecessary that can kill you. The risk of death is about one in a thousand.[16]

Dr. Harlan Krumholz, a cardiology professor at Yale who was not involved in the study, said that the findings contain a lesson for doctors treating heart patients. "When people are making decisions, it's important to disclose to them that this procedure - outside of an emergency - is not known to be lifesaving or to prevent heart attacks ... The vast majority of people who have this procedure have the expectation that it will help them live longer. That belief is out of alignment with the evidence."

Angina is often the symptom that convinces doctors and patients that medical therapy is not enough and that a stent is required. Yet, in this review, 29% of people who had a PCI still had angina, compared to 33% of those on medication - an insignificant difference.[16] One of the authors declared that, "interventional cardiologists use the analogy of a pipe blocked in a house — it's a terrible analogy, but patients accept it. It's simplistic and erroneous."

But what about those who *really, really* need stents - those with seriously blocked coronaries? Well, again the data are disappointing. The first truly placebo controlled trial was published in November 2017.[18] Researchers inserted catheters in all 200 patients but only stented half of them. All patients had severe (≥70%) single-vessel stenoses. The primary outcome was quite ridiculous: exercise time. Yet that utterly irrelevant outcome is recommended by both the US and the European drug regulator. Stenting was not beneficial. The exercise time increased a little more in the stent group, but the difference was not statistically significant, 16.6 seconds (95% CI –8.9 to 42.0, P = 0.20). Moreover, the average exercise time was 510 seconds, or 8.5 minutes, before the intervention, which increased by half a minute in the stent group and by a quarter of a minute in the placebo group. So what?

What I described above about stress tests for chest pain - although shocking - is not an example carefully selected among others. I read the story about the US lawyer a few days before I decided

to write this book and thought it might be an interesting example to work with. What I have demonstrated here is how important it is to be clear about the questions being asked. The more specific you are, the better your searches will be and the more likely you will be able to answer your questions, or at least become clear about just how much you need to extrapolate from the information you find.

The story is by no means atypical. Doctors routinely use diagnostic tests, rarely thinking about whether it has ever been demonstrated that the tests are useful, i.e. whether they make any difference to therapeutic decision making, or whether their use leads to more benefits than harms.

The same can be said about many of the interventions doctors employ, in this case stents. Yet this could also simply be a matter of prioritizing profits over patients - or a matter of convenience for the staff, which the next example demonstrates.