Andreas Grüntzig Lecture at the Swiss Society of Cardiology Congress 2015 in Zurich

Percutaneous coronary intervention, not all roads lead to Rome

Bernhard Meier

Cardiovascular Department, University Hospital Bern, Switzerland

Summary

Percutaneous coronary intervention (PCI) started with a first patient in Zurich, Switzerland, treated by Andreas Grüntzig on September 16, 1977. Having been part of that intervention, I enjoy the privilege of taking care of this patient since. He is still enjoying excellent health and needed only two additional percutaneous interventions in his coronary arteries after 23 and 37 years, respectively. PCI saw an unprecedented evolution to today's role as the most common major medical intervention around the globe. As is typical for a success story, many people have been co-builders. Even more people have tried to contribute to PCI or even replace it with modifications or alternatives that do not benefit patients. This was not always recognised immediately but the only real breakthrough, the coronary stent, was finally recognised by all as the only necessary adjunct to the initial balloon. The achieved degree of perfection of PCI will make it hard, if not impossible, to improve upon it by a change of paradigm, while small adaptations will continue to be introduced because they do not need randomised trials for approval.

Key words: percutaneous coronary intervention; coronary artery disease

How it all began

The first diagnostic arterial procedure goes back to Stephen Hales. In 1726 he measured live arterial blood pressure in a supine horse using a brass glass tube assembly held erect to assess the maximum hight of the systolic blood column. It was 241 cm, corresponding to 186 mm Hg. The introduction of X-ray by the Zurich University graduate Wilhelm Conrad Röntgen in 1895 allowed the first contrast angiogram, performed in 1896 in a human cadaver hand by Victor Teichmann with a mercury containing contrast medium.

Werner Forssmann introduced human cardiac catheterisation by conducting a self-experiment in 1929. He inserted a thin rubber catheter, used at the urology department he was working for, from a cut-down in his left cubital vein into his right atrium. This was not only the first invasive procedure in cardiology but also an ambulatory one as he walked to the X-ray department to shoot what became a historical picture: the catheter with its tip residing in his heart. Diagnostic cardiac catheterisation was born and was first used for pressure measurements by André Cournand. They were endowed jointly with the Nobel prize in 1956.

Percutaneous coronary interventions (PCIs) were a logical extension of selective diagnostic coronary angiography, first performed by Mason Sones in 1958. Although this ground-breaking diagnostic study occurred inadvertently when an end-hole catheter used for a contrast aortogram slid into the ostium of the right coronary artery, and in spite of the fact that prolonged but self-limiting asystole occurred in the patient, it laid ground for what we know today as coronary angiography. Active coughing by the patients initially bridged asystolic phases after each coronary injection until the advent of modern contrast media no longer inducing bradycardia. It took seasoned angiographers years to break the habit of having the patient cough after each injection. More recent endeavours to replace classical coronary angiography by contrast examinations with computed tomography (CT) or magnetic resonance imaging (MRI) have created significant industrial volume without, however, advancing the field. The unsurpassed ticket conventional coronary angiography with *ad-hoc* PCI prevails and is performed in millions of patients around the globe every year.

PCI, the most significant Swiss contribution to medicine of all time

Based on Mason Sones' coronary angiography technique, the possibility to access the systemic circulation with larger catheters through the femoral arteries introduced by Melvin Judkins, and a catheter-based technique of improving arterial vessel stenosis by dilating them with catheters of increasing diameters put forward by Charles Dotter, Andreas Grüntzig developed balloon angioplasty which was initially called percutaneous transluminal angioplasty (PTA). In contrast to Werner Porstmann, who was also working on this idea in Berlin, East Germany, Grüntzig found a solution to render balloons form-constant and pressure-resistant. Latex balloons of the time could not withstand pressure. They rather grew in size. Porstmann tried to con-

tain that by longitudinally splitting a plastic catheter and inflating the balloon inside it. While this did resist pressure in a usable oval shape, balloon deflation resulted in catching the dissected arterial wall while the slits were closing. Making the slits larger resulted in protrusion of balloon segments. Grüntzig found help from a retired plastics expert at the Technical University just across the street from the University Hospital of Zurich where Grüntzig was working in the Division of Angiology. Polyvinyl chloride could be heat treated to meet the requirements for balloon angioplasty. There was no industrial production site at hand, so Grüntzig used his kitchen stove to produce prototypes which then were directly used in humans. This shortcut approach was still possible at that time and certainly to the benefit of the method and the patients. PTA appeared less traumatic for the patients than the Dotter technique, and it was. Grüntzig had also tried a stiff wire with an oval bend close to the tip. He connected it to a household drill for rapid revolution and pulled it backwards through a narrowing, executing some thrombectomy or atherectomy with the thrashed material being embolised to the periphery. This was a dog experiment and never made it to human use.

Being promoted to a staff position in cardiology in what appears to be the world's speediest career of any cardiologist, i.e., virtually no training in cardiology, miniaturisation of this equipment and application to the coronary arteries became first priority. This required industrial machines and the Schneider company took over the balloon catheter production. The first coronary balloon for what was initially going to be called percutaneous transluminal coronary angioplasty (PTCA) and subsequently percutaneous coronary intervention (PCI) was not fed over a guide wire like the peripheral dilatation balloons. As fluoroscopy resolution was poor at that time and still frames or even replay were not a feature yet, Grüntzig needed distal pressure measurements for immediate assessment of the effect of PCI. Only the processed 35 mm cinefilm had adequate resolution to see the lumen and dissection flaps. However, it was highly unpractical to repeatedly stop the procedure for processing the cinefilm, which took about 20 minutes. In addition to the lumen for pressure measurement, a lumen for balloon filling was required and there was no room for feeding a wire through the shaft on top of that. This balloon was not steerable, but other than that it could still be used nowadays, at least for a proximal PCI. While the balloon was tested in dogs and ready in early 1976 for a first human case, it was not until September 16, 1977 that PCI was finally performed in a patient for the first time worldwide. Even several trips to the United States (USA) to find a first patient had been futile. At the time, both in the USA and, much more, in Europe, indications for coronary angiography were very restrictive. Patients usually had to have experienced long periods of angina pectoris refractory to multiple drugs, which usually included a history of one or more myocardial infarctions, before they were considered for invasive work-up. Just about never did this then reveal single-vessel disease, let alone a proximal discrete stenosis such as Grüntzig was looking for. Grüntzig was just returning from another trip to San Francisco, California, USA, again quite frustrated at not finding a suitable patient, when I presented him with a 38-year-old man (the same age as Grüntzig's), who had been suffering from daily angina attacks for several weeks, was put on a bicycle ergometer (not quite what would be done today), and was found to have severe ST-segment elevation, ventricular tachycardia, and chest pain during exercise. An exception was made and he was subjected to coronary angiography revealing a single proximal stenosis of the left anterior descending coronary artery (LAD). Coronary artery bypass grafting (CABG) was scheduled, but I was the resident responsible for him and I had a better idea. Grüntzig was utterly pleased with the case and took me to the patient on the spot to obtain oral consent. Quite bluntly he told the patient that he was going to try something that had never been done in humans but worked in leg arteries and had also worked in dogs, and that there was a risk that immediate CABG would become necessary if it did not work out. The patient still recalls this conversation and how he immediately trusted Grüntzig and found nothing wrong with at least a reasonable chance to avoid open chest surgery. The procedure was performed the next day, as Grüntzig had obtained the necessary nods from the head of his department and the head of the Department of Cardiac Surgery long ago. The crowd attending was not really a crowd but rather a handful. Surgical stand-by (drop-by actually) was inaugurated with that case as two cardiac surgeons dropped in and out during the procedure. The patient tolerated the balloon inflation well and the lesion was remedied, yielding what would nowadays be called a stent-like result. The patient left the catheterisation laboratory with a transient right bundle branch block which recurred during a thallium exercise stress test two days later, which also revealed some, but improved, ST-segment elevation and reduced thallium uptake. It was thought at the time that this was a normal finding after PCI. I was never to see anything like that again and I doubt that Grüntzig was. The patient is still alive and well, now 76 years old. He had two additional episodes

of chest pain, one 23 years after the procedure requiring first a bare metal stent (BMS) close to the initial lesion and a few months later a re-dilatation for in-stent restenosis, and one at 37 years requiring a drug-eluting stent (DES) again in the vicinity of the initial lesion plus one in the proximal part of the right coronary artery. Figure 1 shows the milestone angiograms of this historical patient. Exercise stress tests the day after this last procedure and 6 months later were normal and the patient still enjoys life without physical restrictions. While he had not taken any drugs for decades after his first procedure, he now accepted the idea of a lifelong single antiplatelet compound and a statin, in spite of his conviction that drugs taken chronically lost their effect.

The indications encompassed from the beginning primarily single vessel disease, more rarely double vessel disease, and only exceptionally triple vessel disease with a maximum of three to four discrete proximal coronary lesions. The left main stem was initially included but then banned for many years for all the wrong reasons. Two of the initial left main stem patients died within a few months of follow-up. Although their lesions were found patent at autopsy and the reasons for their demises remained unclear, it was assumed that PCI for the left main stem was not safe. Now with stents, in particular the refined DESs, left main stem indications have returned for good. Randomised trials between PCI and CABG have confirmed iteratively that indications were appropriate from the

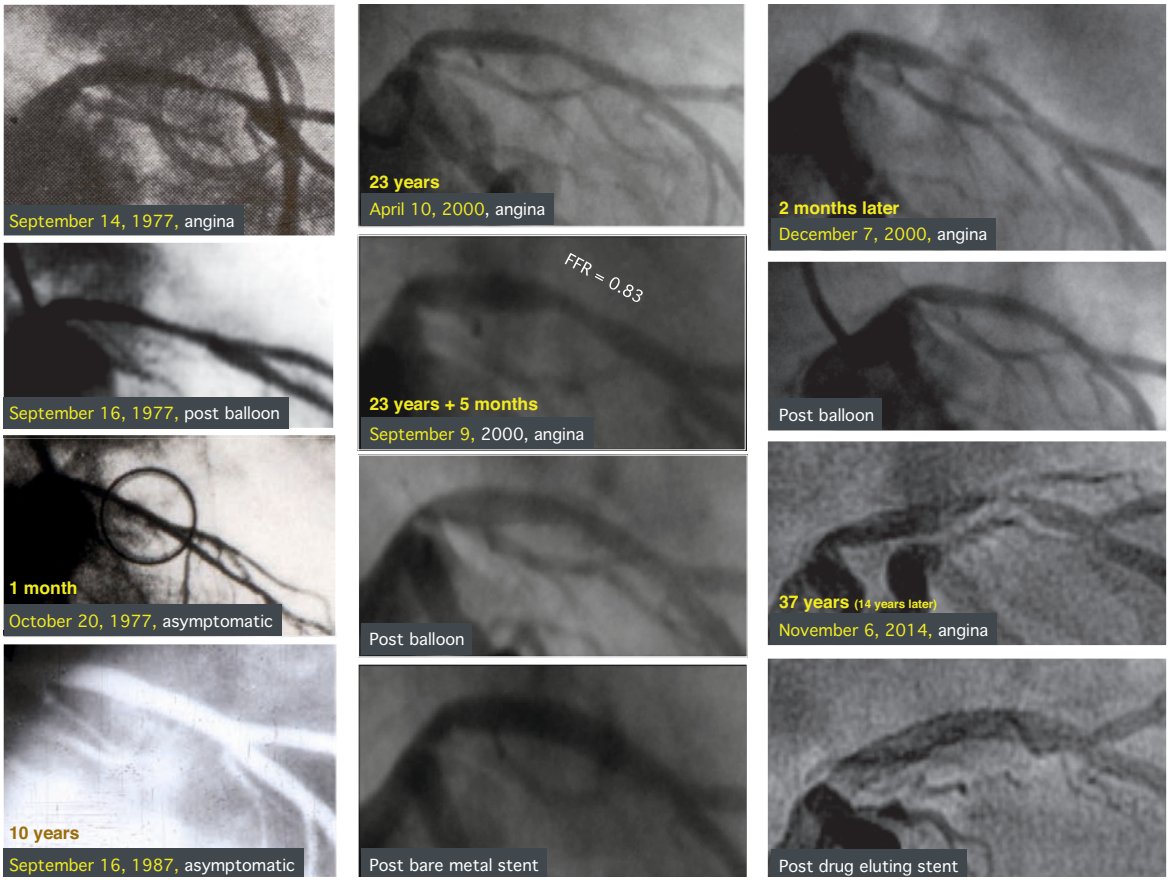

Figure 1

PCI number 1 in the world (a man, 38-year-old at the initial and 75-year-old at the latest procedure). The pictures have to be read in chronological order first left top to bottom, then centre to bottom, and finally right top to bottom. The lesion shown on April 10, 2000 in an angiography indicated by angina would normally have been a perfect indication for PCI to me. In this particular case I preferred to refrain from angioplasty, not to spoil the so far perfect story, albeit the lesion was slightly more proximal than the original one. The patient kept his symptoms and insisted on having treatment. Thus the angiogram was repeated on September 9, 2000. To find an excuse again not to dilate, I performed the only clinical fractional flow reserve (FFR) measurement in my career and used the normal result to convince the patient that he needed no treatment. However, he insisted and got a reasonably good balloon angioplasty result which I would have accepted had he not insisted on a stent. It took only a few weeks for an in-stent restenosis to develop (drug-eluting stents [DESs] were not yet available) which had to be re-dilated. Another 14 years later a new lesion somewhere in-between this stent and the original site caused angina again and was stented, this time with a DES. At the same time the right coronary artery also received a DES (not shown).

beginning and that pushing the envelope to advanced and highly complex multivessel disease was beyond the scope of PCI and still is [1, 2]. On the other hand, reports advocating a conservative attitude in early coronary artery disease [3, 4] are misleading, as exemplified by figure 2. In particular, the use of fractional flow reserve (FFR) for clinical indication may not be best for the patient. With a pathological FFR, PCI will ensue and the FFR measurement could have been spared. With a normal FFR annulling the indication for PCI, a chance for at least symptomatic if not prognostic improvement may get missed (fig. 3) [5].

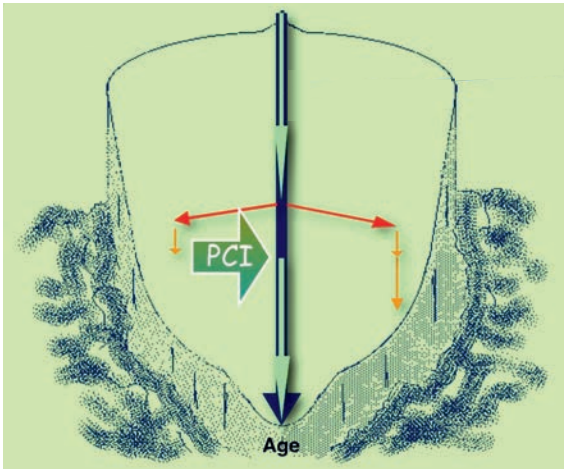

Figure 2
Metaphorical depiction of coronary artery disease and the role of percutaneous coronary intervention (PCI). Life can be looked at as a slow but relentless forward motion on a high plane. Staying close to the centre line assures the longest life. Coronary artery disease (red arrow) as many other diseases can deviate the patient from the safe centre line. Not treating it because the patient is stable and alive (right hand side) clearly has an inferior prognosis compared to treating it with PCI (left hand side). The studies merely looking at whether the patient is stable and alive [3, 4] are short-sighted. This is even more true if additional disease deviates the course even further towards the abyss. Close to the precipice, coronary artery bypass surgery often is the only way to prevent premature demise if at all.

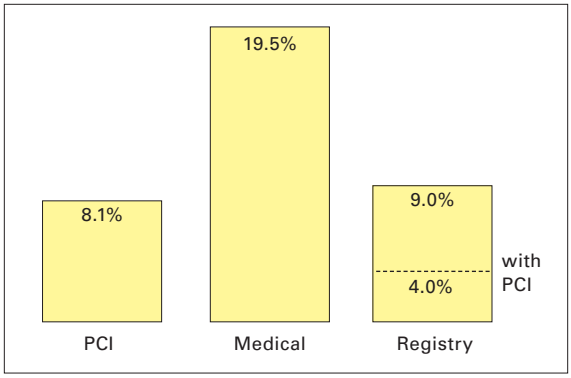

Figure 3
Endpoint events (mainly need for percutaneous coronary intervention [PCI]) in the FAME-2 trial at 2 years [5]. Of 1220 patients, 888 had a pathological fractional flow reserve (FFR) value of the coronary lesion of interest. They were randomised to PCI or medical treatment (Medical). The remaining 332 patients (Registry) with a normal FFR (>0.80) were treated medically. The graph shows that PCI in patients with a pathological FFR effected a drastic reduction (to less than half) of events. The dashed line in the right column hypothetically indicates what could possibly have been achieved if the patients with a normal FFR had not been deprived of PCI.

Alternatives and complements to PCI

Table 1 depicts what has emerged, has been tested, and has at least temporarily been adopted as replacement for or complement to the balloon catheter since the inception of PCI. In the 1980s, almost simultaneously coronary stents were introduced mainly in Europe and atherectomy devices mainly in the USA. It was immediately apparent to the critical user of both so-called new devices that the stent had tremendous potential. It remedied the worst flaw of PCI, namely obstructive coronary dissection with subsequent abrupt vessel

Table 1: Equipment for percutaneous coronary intervention.

Standard
Balloons
Guide wires
Guiding catheters
Stents (drug eluting)
X-ray
Contrast medium
Heparin
ADP (and GP IIb/IIIa) antagonists
Aspiration catheters
Femoral plugs or sutures
Percutaneous ventricular assist devices
Optional
Distal protection devices
Rotablation
Drug eluting balloon
Absorbable stents
Optical coherence tomography
Intravascular ultrasound (2 or 3 dimensional, Doppler)
Fractional flow reserve
Direct thrombin inhibitors
Obsolete
Directional atherectomy
Brachytherapy
Drugs against restenosis
Angioscopy
Not recommended
Laser
Stem cell therapy

Sequence within category as per importance.
ADP = adenosine diphosphate; GP = glycoprotein.

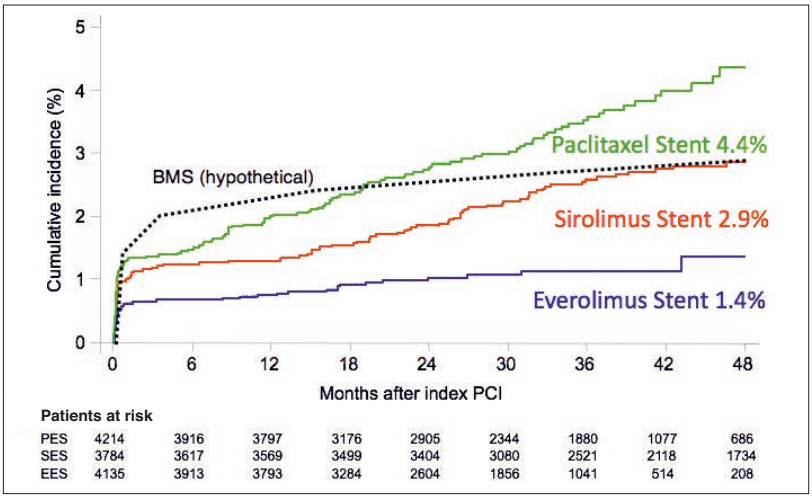

Figure 4
Stent thrombosis after percutaneous coronary interventions (PCI) from controlled trials of the early drug-eluting stents (PES: paclitaxel-eluting stent, SES: sirolimus-eluting stent) and a current drug-eluting stent (EES: everolimus-eluting stent) [10] compared with an added (hypothetical) stent thrombosis curve of modern bare metal stents (BMS). Already the early DESs (drug-eluting stents) had a lower stent thrombosis rate than BMS during the first year, only the PES had an inferior outcome at 4 years compared to a BMS.

closure. Atherectomy remedied nothing but promised a better long-term result. The promise did not materialise. An exception is rotablation, which to the present day solves problems where the balloon cannot pass or fails to crack a circumferentially calcified lesion. These cases, however, have become exceedingly rare with the ever lower profiles of balloon catheters and their ever growing pressure resistances (currently more than 40 bar).

The reason why it took a while until the superiority of the stent over other new devices was also recognised in the USA lay in one of the many misinterpretations of data in the history of PCI. As stents were initially used exclusively as bailout devices, the outcome of stented patients was significantly worse than the outcome of elective PCI patients without stents [6]. Laser and atherectomy on the other hand were used electively and preferably in patients with large coronary vessels, which were less prone to abrupt closure. Although their outcome was not better than balloon-alone treatment, it was superior to the stent results of the bail-out patients. Looking at when stents and other new devices were used during live-cases and what their results were [7] and a publication promoting rational behaviour [8] helped to eventually set things straight.

Irrational use of drug-eluting stents

When DESs were introduced in the first years of this millennium, another misinterpretation of data led to irrational behaviour for many years [6]. Initially, things were alright when the drastic reduction of restenosis was highlighted and only the stiff price prevented people from using DESs exclusively. Then a bane of the early DESs that had been predicted [9] was picked up and reported out of context, and its proportion and importance were tremendously blown up. The early DESs were apparently somewhat overdosed and only permitted a very thin tissue coating of the stent struts over time. This then allowed erosion of the coating after the first year of follow-up leading to a stent thrombosis rate over the subsequent years at around 1% per year which was significantly higher than that of BMSs. While it was correct to point that out and caution about intensifying long-term antiplatelet treatment in patients with DESs, it was erroneously assumed that this also pertained to the early period. In fact, during the early period even the first generation DESs had a significantly lower stent thrombosis rate than BMSs, irrespective of the intensity of antiplatelet therapy. So for the past almost 10 years, patients with a high risk of stent thrombosis (poor compliance with antiplatelet drugs, need for interruption of antiplatelet therapy for planned surgery soon after PCI, etc.) typically received a BMS when they should have received a DES. Even the lower stent thrombosis rate of BMSs after the first year did not compensate for the higher stent thrombosis rate with BMSs during the first year for many years of follow-up. Moreover, current generations of DESs have an even lower stent thrombosis rate during the first year, again irrespective of the intensity of antiplatelet therapy, and even increase that advantage over BMSs during long-term follow-up (fig. 4) [10].

The current use of modern DESs in all indications on the basis of a flurry of data comparing DESs to BMSs in various settings, affords a demonstrable survival benefit with PCI compared with medical treatment for the first time in the history of PCI [11]. The initial PCI before the introduction of the BMS had been close to that goal but then the use of BMSs temporarily worsened outcome owing to the new problem of stent thrombosis. Initial DESs improved it somewhat but only current DESs achieved a significantly reduced mortality.

Future modifications of PCI

It is uncontested that more stringent control of risk factors by behavioural measures and statins reduces the age-corrected prevalence of coronary artery disease. Nonetheless, with the ever increasing average age of western populations, demand for coronary revascularisation will stay high. Early coronary angiography is already a standard. Alternative imaging techniques

such as CT or MRI can easily be skipped, as coronary angiography is nowadays available instantly virtually everywhere and its risk, amount of contrast medium bearing some renal toxicity, X-ray exposure, and overall inconvenience are comparable to if not lower than that of CT. This is independent of whether the femoral or the radial approach is selected. In fact, the femoral approach should remain the standard, as the radial approach is fraught with a chronic occlusion rate of the used radial artery of about 5–10% [12]. Smaller catheters would improve on that but they make the radial technique even more intricate and the learning curve for operators even flatter. It does not appear justified to impose the significantly longer learning phase, the need for crossovers, and the risk of permanently occluding the radial artery on patients unless they demand it fully cognizant of these downsides.

Another myth is that absorbable stents, currently referred to as bioabsorbable vascular scaffolds (BVSs), improve the late outcome in terms of reduction of late stent thrombosis, resumed normal vasoactivity of the coronary artery, and normalisation of future access points for CABG. First, the current models are far from the ideal absorbable stent that would disappear within a few weeks without any local inflammation and without having chunks not opposed to the wall (e.g., overstented side-branches), embolising distally during the resorption process. They are also far from the ease of use, visibility, hoop strength, and economical production costs of current DESs. Using a current BVS implies struggling during implantation like in the early BMS years, risking a higher early complication and restenosis rate, and hoping for a completely normalised vessel in the future. The latter is as unlikely to happen as the reconstruction of necrotic myocardium by injection of stem cells meant to not only reconstitute muscle cells that align properly but also to rebuild their vascular support and electrical connectivity. Why not admit that we have reached a standard of PCI that may still be several percentage points below perfection, but that is hard to improve upon. Things that might look promising while being on the horizon are unlikely to prevail, be that because of lack of superiority or just because of the lack of proof of it. Small as any further advantage can only be, randomised trials with thousands of patients and prolonged follow-up will be required to prove them and paying for that may not be attractive and not even make sense. Once arrived in Rome you can easily cope with the fact that not all roads lead to Rome.

Correspondence:
Bernhard Meier, MD
Professor and Chairman of Cardiology
Cardiovascular Department
University Hospital Bern
CH-3010 Bern
Switzerland
bernhard.meier[at]insel.ch

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

References

1 Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet. 2013;381:629–38.
2 Dangas GD, Farkouh ME, Sleeper LA, Yang M, Schoos MM, Macaya C, et al. Long-term outcome of PCI versus CABG in insulin and non-insulin-treated diabetic patients: results from the FREEDOM trial. J Am Coll Cardiol. 2014;64:1189–97.
3 Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356:1503–16.
4 Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol. 2010;56:177–84.
5 De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367:991–1001.
6 Meier B. The infamous coronary stent saga. Cardiovasc Med. 2014;17:239–44.
7 Chatelain P, Meier B, Friedli B. Stenting of superior vena cava and inferior vena cava for symptomatic narrowing after repeated atrial surgery for D-transposition of the great vessels. Br Heart J. 1991;66:466–8.
8 Meier B. New devices for coronary angioplasty: The Emperor's new clothes revisited. Am J Med. 1995;98:429–31.
9 Togni M, Windecker S, Meier B. Treatment of Restenosis. Curr Interv Cardiol Rep. 2001;3:306–10.
10 Räber L, Magro M, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation. 2012;125:1110–21.
11 Windecker S, Stortecky S, Stefanini GG, da Costa BR, Rutjes AW, Di Nisio M, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. BMJ. 2014;348:g3859.
12 Lim LM, Galvin SD, Javid M, Matalanis G. Should the radial artery be used as a bypass graft following radial access coronary angiography. Interact Cardiovasc Thorac Surg. 2014;18:219–24.