Opinion article

A personal perspective of the development of percutaneous coronary interventions

Una perspectiva personal del desarrollo de las intervenciones coronarias percutáneas

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Keywords: *stents, coronary angioplasty, percutaneous interventions, bare metal stents, randomized clinical trials.*

Palabras clave: *stents, angioplastia coronaria, intervenciones percutáneas, stents metálicos desnudos, ensayos clínicos aleatorios.*

Revista Argentina de Cardioangiología Intervencionista 2023;14(3):118-122. https://doi.org/10.30567/RACI/202303/0118-0122

BRIEF HISTORY

The development of percutaneous coronary interventions has been heady and fascinating. However, any attempt at summarizing its history is fraught with risk of oversimplification and omission. Having had the opportunity to interact with pioneers who personally inspired me, makes me reflect about a pattern in the process involving novel ideas followed by systematic development. Having been born in a time fairly ignorant of the risks behind the main cause of death, gives me a vantage point to appreciate the progress achieved thus far. Also, a perspective of how much work is still needed.

In medical school in the 60's, doing hospital rounds as a student following professors, I witnessed the impotence doctors faced, while hovering over victims of heart attack. A common problem whose magnitude and root causes were not yet gleaned. Considering fundamental individual contributions to current progress I reflected on the critical ones, without which the following step would not have materialized.

Enter Andreas Gruntzig and his revolutionary new method. It did not take long for everybody to notice that percutaneous balloon dilatation of coronary blockages was amazingly simple and potentially disruptive of the status quo. Without repeating comprehensive analyses of his life and work[5], I will only refer to my experience meeting him in Feb 1978, just a few months following his first human PTCA. It was at his presentation at the SCVIR annual meeting in New Orleans. It was my first medical congress in the US during my first year of residency and I was prompted by my late mentor and president of the SCVIR that year, Stewart Reuter, that I should not miss this talk. So, I sat early in first row with anticipation. Gruntzig was a very young, dynamic speaker who struck me as bright, sincere and cautious. By then, he had performed only four coronary cases and had one death due to abrupt coronary closure. He spent significant time showing pathology slides of the occluded coronary artery and, analyzing the reason of the complication. He recognized that the crude nature of the PTCA balloons was a problem and, cautioned against the low burst pressure limit of the device. He also pointed at the unpredictability of the vessel response to intraluminal dilatation and offered the analogy of a foot pressing on fresh snow as favorable lesion response and, stiff rubber for the unyielding ones. Charles Dotter, from whom he draw inspiration[5], was in the audience.

Gruntzig recognized Dotter's coaxial catheter angioplasty as a primer of his interest in the subject but his non-compliant intraluminal balloon was a giant step toward practical PTCA. Interestingly, his emphasis on the dreaded balloon-induced abrupt coronary closure elicited in my mind the idea of the need for a scaffold to hold in place disrupted plaque material. An idea which followed me out that room and for the rest of my life[6]. A similar scenario happened during a presentation of the balloon expandable intraluminal stent I gave in Arizona in the early 90's when another young investigator, Henning Andersen, conceived of mating a biological cardiac valve on a balloon expandable stent scaffold[7].

THE CURRENT PROBLEM

The review of the state of heart disease and stroke statistics-2023, by the American Heart Association[8], casts a light on the current global status of cardiovascular disease. A glance at the world cardiovascular mortality map (**Figure 1**) shows great disparities.

However, the problem in the Americas is relatively less severe compared with Central Asia, the Balkans, the Middle East, South-East Asia and most of the African Continent. The curve of US cardiac deaths from the 1900's to 2020 in this report, allows pinning landmarks that reflect the historical evolution of the disease **(Figure 2).**

1- The great World Wars had a broad socio-economic impact on CV risks that may have resulted in the rise of CV deaths from 1920-1950.

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Presented at the Salon Libertador del Palacio San Martin, Buenos Aires, Argentina "Dia Internacional de la Cardiologia Intervencionista" Septiembre 15, 2023

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No conflicts of interest whatsoever.

Received: 04/10/2023 | Accepted: 16/10/2023

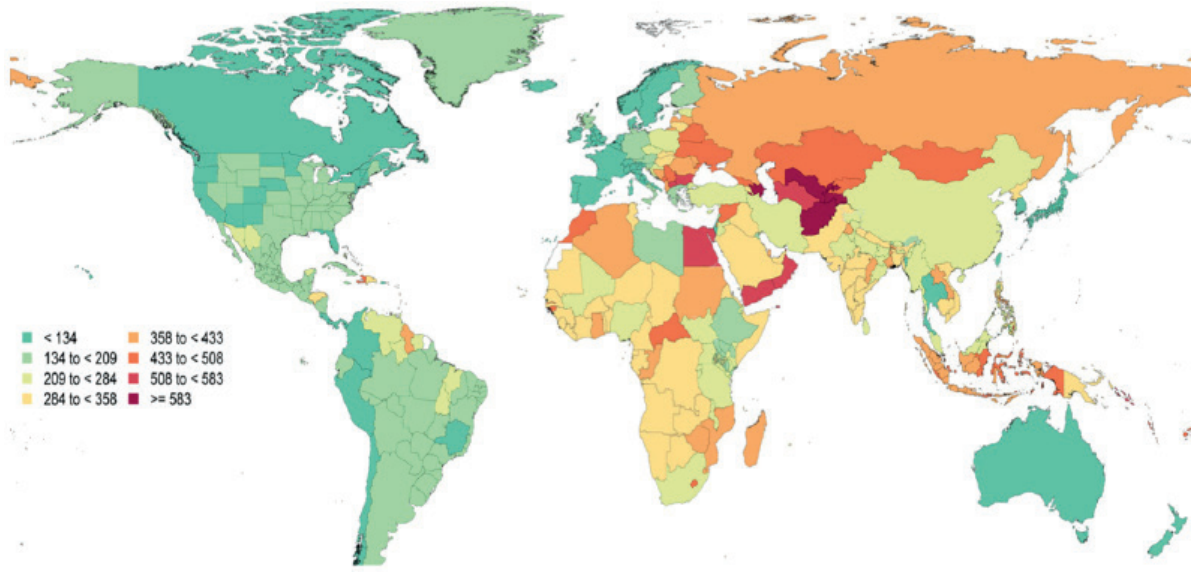

Figure 1. *From the American Heart Association. Deaths per 100 thousand population (Ref 8).*

2- The acknowledgement of the deadly CVD epidemic motivated the Framingham Heart Study starting in 1948 and is ongoing today.
3- This resulted in public awareness of the major risk factors of CVD.
4- Awareness motivated the development of corrective measurements both in prevention and therapy during the mid-sixties to the turn of the millennium.
5- As a result, there was a clear decline in the incidence of CV deaths from the year 2000 onward. The rise observed from 2010 is due to the curve not being adjusted for age. The increased survival, pushed the highest incidence of CV mortality both in men and women to the group aged 80 and older. The higher female CV mortality prevalent in the 1985-2010 period yielded to higher CV mortality in men in 2013 to the present. This was the result of renewed emphasis in the prevention and care of female CVD and the elimination of common misconceptions such as pre-menopausal hormonal protection **(Figure 3).**

Analyzing CVD with other major causes of death in the US in 2020, shows the clear prevalence of CVD compared to cancer, accidents, diabetes mellitus, chronic renal disease, Alzheimer's, and homicide, Covid-19 deaths this year constituted the third cause of death in the US **(Figure 4).**
But when we look at CV deaths by category, coronary heart disease remains the largest component by far **(Figure 5).**

DEVELOPMENT OF CORONARY THERAPY

Since the advent of balloon angioplasty in 1977, there was a steady growth in trained operators. Proliferation of cardiac catheterization laboratories extended to medium sized hospitals and the organization of emergency mobile response and telemetry facilitated the role of stand-by cardiac emergency units. Progress in the quality of imaging equipment and catheterization material ensued as a result. The approval of the Palmaz-Schatz stent in 1994 coincided with a change in the rate of these growth trends **(Figure 6).**

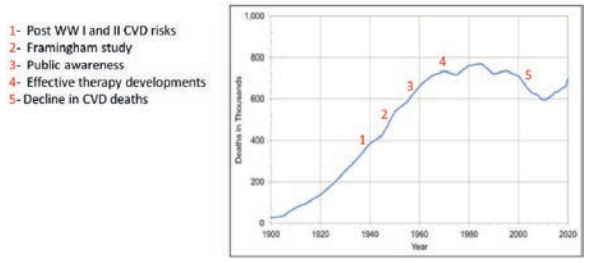

Figure 2. *Adapted from the American Heart Association (Ref 8).*

LANDMARKS IN PCI

A personal view on which were the major steps in the history of percutaneous coronary interventions (PCI) **(Table 1)** points to Gruntzig's first case as the very beginning in October 1977. It also marks the end of an era, as clinical experimentation would soon become increasingly more difficult and extensively regulated.

BALLOON PTCA VERSUS BALLOON-EXPANDABLE METALLIC STENT

The simultaneous report of the BENESTENT and STRESS trials in 1994[9,10] were first to demonstrate the superiority of stents over balloon-PTCA at 6 months. These were landmark trials because they were the first in complying with the new rule of the FDA requiring vascular implantable devices to be approved following RCT's (randomized controlled trials). This marked a new era in which approval of implantable vascular devices would be lengthy and costly, requiring greater financial investment and greater sacrifice for patients and investigators.
Soon after approval of the metal stent, it became evident that in-stent restenosis was a significant problem that would require further development.

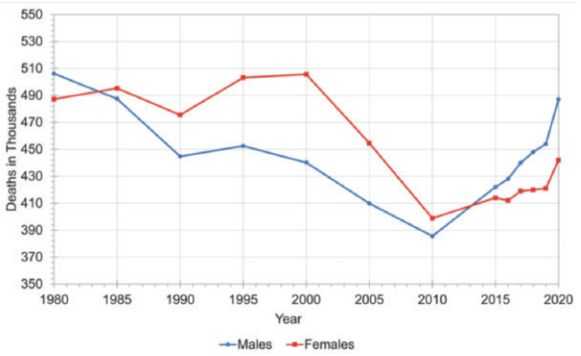

Figure 3. *Cardiovascular mortality trends for US males/females From the American Heart Association (Ref 8).*

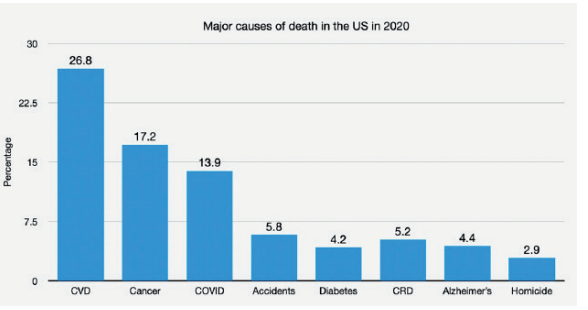

Figure 4. *Reproduced from the American Heart Association (Ref 8).*

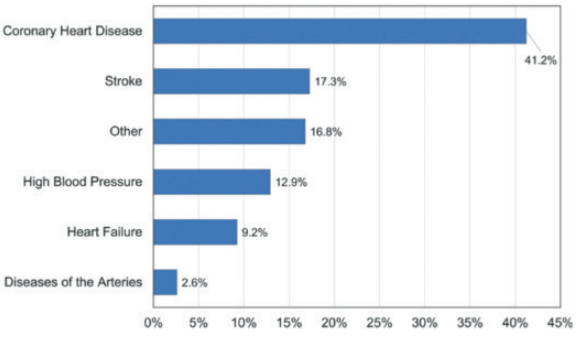

Figure 5. *Reproduced from the American Heart Association (Ref 8).*

THE DRUG ELUTING STENT

The advent of the drug-eluting stent was a relatively quick solution that proved very effective. In 2002 an RTC comparing a sirolimus DES with a bare metal stent showed convincingly that 6 months restenosis and major cardiac events were reduced very significantly[11]. With a seemingly more effective tool, the application of the coronary stent increased beyond STEMI to severe chronic coronary ischemia. This motivated questions of durability of PCI-stents in patients with large coronary atherosclerotic burden compared with coronary bypass graft surgery (CABG).

PCI VERSUS SURGERY

Patrick Serruys, who was a leader in the previous pivotal trials undertook the task of comparing by RTC, PCI vs CABG in severe coronary artery disease (SYNTAX)[12]. By 12 months following randomization death, stroke or MI were similar but repeat revascularization was significantly lower for CABG, suggesting better durability for the later. Furthermore, comparing major adverse cardiac or cerebrovascular events between both therapies, CABG was significantly lower than PCI. However, when the degree of coronary atherosclerotic burden was categorized by a numeric score (SYNTAX Score), lower and intermediate score groups showed no significant difference in major adverse cardiac or cerebrovascular events. The group with a high score fared significantly better with surgery thus establishing a definite criterium for patient selection.

It was noted, that most of the patients in the PCI group received bare metal stents, posing the question if different results would be obtained should DES be compared to surgery. This conundrum was addressed in a later study in a more critical application such as the left main coronary artery disease. The EXCEL trial[13] was extended to 5 years comparing PCI-DES and CABG in patients with low or intermediate anatomical complexity and found no significant difference in the rate of death, stroke, or MI.

MEDICAL THERAPY WITH OR WITHOUT INTERVENTION

Throughout all these studies, overall survival remained relatively unchanged irrespective of therapy. Many questioned the need for revascularization in patients on so called optimized medical therapy (OMT) arguing that incidence of mortality and new MI would be the same. As early as 1997 many RTC's compared patients on OMT alone vs OMT plus PCI or surgery on intention-to-treat basis[14-24]. As observed by a recent systematic review[25], all-cause mortality was not significantly different between medical therapy alone compared to medical therapy plus intervention but, there was a lower risk of spontaneous MI with the later. The risk of stroke was not different between therapy groups but relief of angina pectoris was consistently more effective for the group involving PCI or surgery. The obvious consideration is the value of a superior quality of life and productivity for those undergoing revascularization. It is also of note that most of these trials had a very significant bi-directional cross over.

The so called OMT drug treatments for stable CAD involve rather traditional drugs, most of which are old and have become generic. Despite their long-proven effectiveness and safety, some drugs have significant adverse effects and relatively low therapeutic index[25]. Currently, there are many new drugs that potentially could change the landscape of therapy both for primary and secondary prevention. Most salient are the PCSK9 inhibitors as monoclonal antibodies and RNAi's. Drugs in these groups have been approved on the basis of being very effective in lowering LDL but its translation into CVD benefit is yet to be demonstrated. However, preliminary evidence of plaque regression suggests an import role in the future[26]. A novel LPa inhibitor Muvalaplin, is an oral drug which also very effective in lowering this independent risk factor for plaque formation and aortic valvular disease. Other biological drugs such as the glucosuric agents SGLT-2 and the glucagon-like receptor agonists GLP-1RA offer promise in addressing two important risks for CVD, obesity and type-2 DM. Older drugs like Icosapent ethyl and the uricosuric drug Colchicine look like intriguing new additions for their anti-inflammatory proper-

Figure 6. *Source: Hospital Care Statistics Branch, National Center for Health Statistics. Centers for Disease Control and Prevention (CDC)*

1977	Gruntzig first balloon PTCA (1)
1994	Balloon PTCA vs BMS (BENESTENT, STRESS) (9-10)
2002	BMS vs DES (RAVEL) (11)
2009	PTCA-Stents vs CABG (SYNTAX I-III, EXCEL) (12)
2007	PTCA-stents vs OMT (COURAGE, ISCHEMIA) (17,24)
2013	DES vs bioresorbable stent (ABSORB I-IV) (29-30)
2019	Complete vs culprit vessel revascularization in STEMI (COMPLETE)(34)

Table 1. *Significant landmarks in the development of percutaneous coronary angioplasty-stents Statistics. Centers for Disease Control and Prevention (CDC)*

ties[25]. Problems in implementing these new drugs and others to come, include time and cost. Whether they will constitute ultimate game changers, will take many years to find out. In the meantime, the main focus is in lowering LDL-C in secondary prevention and primary prevention in those with qualified risk. The current AHA-ACC guidelines for optimal LDL level is a 30% reduction of current baseline level or 70 mg/dl. The ESC recommends 50% reduction from baseline or 55 mg/dl[27]. Given the acceptable safety and effectiveness of these modern agents, I would not be surprised if the guidelines are revised in the future to recommend 70% reduction from baseline or 30 mg/dl.

THE BIORESORBABLE STENT

The advent of the bioresorbable stent (BRS) enjoyed wide support from the interventional community with expectations of acting as scaffold supporting flow and disappearing in a few months, providing sustained patency and vaso-motility[28]. No other stent ever had so many trials to eventually fail. In fact, the FDA approval was based on the proof of narrow equivalency to a metallic DES[27]. After a several months following approval in 2016, the manufacturer withdrew the device from the market in 2017. Two meta-analyses comparing the BRS to a metallic DES showed unfavorable risk-ratio for target lesion failure and also for definite or probable stent thrombosis[30,31]. However, the bioresorbable stent is not gone and trials continue to explore the potential of older and new materials[32,33].

COMPLETE VERSUS TARGETED REVASCULARIZATION

Recent RTC's in patients with STEMI compared PCI-stent revascularization of the artery leading to the infarcted area or "culprit" vessel, versus complete revascularization of any significant additional coronary lesion (stenosis ≥70%, FFR ≤0.80). The composite end-point of CV death, new MI or revascularization was significantly different between study groups by a substantial difference[34]. This is a provocative new concept that could motivate reassessment of the role of PCI in severe chronic ischemia.

Of interest is the fact that in its early years, the use of the stent was cautious, following a minimal use rule. This was best illustrated by the famous "oculo-stenotic reflex" remark used to criticize the seductive persuasion of smooth contours attained by stenting![35] Regardless, complete revascularization should only be applied after proper clinical judgement, physiology guidance and intracoronary imaging, taking advantage of the markedly improved PCI materials and methods we have available today compared with those in the late 90's.

THE ERA OF PROTOCOLS AND MANAGEMENT GUIDELINES

Guidelines are useful and help the doctor in the decision making process. However, they also confine practice into rigid frameworks. Not to follow societal recommendations may affect reimbursement by insurance companies and may pose a legal malpractice liability. Sometimes these guidelines and protocols reflect standards of practice at a given time in history and become obsolete with the advent of new resources and discoveries. On the positive side, adherence to established protocols protects the rights of the patient, the doctor and the institutions. In the past few years we had new guidelines on the management of chronic coronary ischemia[36,37], valvular heart disease[38], heart failure[39] and cardiogenic shock[40]. The "art" in medicine and the sacred relationship between doctor and patient based on mutual trust, respect and loyalty may be eroded by management protocols. Taken to an extreme, the medical practice may be restricted by computer generated algorithms generating rigid patterns of practice. We hope that will only happen in the fantasy world of novels and movies and the humanistic aspect of our profession will be preserved.

ARE WE WINNING THE BATTLE AGAINST CVD?

We are making steady progress. But as the patients survive to older age, CVD expresses new characteristics that pose new challenges. Patients are becoming older and more fragile. Co-morbidities affect results, and multiorgan failure and immune decline challenge our expectations for success. Covid-19 caused mayhem before we could figure out the CV complications caused by this viral epidemic and wiped out in one year the gains of years before. The battle against CVD is a battle of attrition. It is slow and is very expensive. New drugs hold promise for prevention, but the need for CV interventions will only increase. Ultimately, the focus should remain in promoting not only a long but also an active, productive and happy life.

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