

Cardiovascular Medicine

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From past to future in cardiovascular care and research in Ticino

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In this article based on the Grüntzig Lecture 2018 the author gives his personal memories and a review of the development of cardiology in the canton of Ticino.

Introduction

I cannot describe cardiovascular care and research in Ticino without mentioning my personal professional life, since in the last 40 years I was one of the leaders in the progression of cardiology in this Canton.

I can divide my professional career into three periods: in Zurich as medical doctor (the Zurich experience), in

Lugano as chief of Medicine at Ospedale Civico (the Ospedale Civico experience) and in Lugano as chief of Cardiology at the Fondazione Cardiocentro Ticino (the Cardiocentro experience) (fig. 1).

The Zurich experience (1963–1971)

In 1963, I obtained my medical degree at the University of Zurich (my *Alma mater*). Then I started a 2-year fellowship at the Pathologisches Institut at Zurich University. I always will remember my mentors in anatomy and pathology – Gian Töndury and Erwin Uehlinger. Over this time, I had the unique experience of precisely determining the cause of death in hundreds of autopsies. That experience

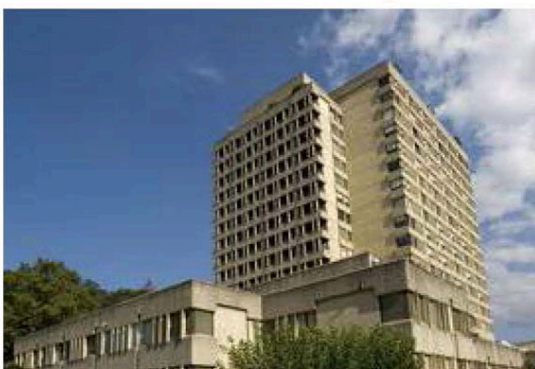
Figure 1: Medical Institutions of my professional life.



Zürich University



Ospedale Civico, 1972



Ospedale Civico, 1980



Cardiocentro Ticino, 1999

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had a great impact in my professional life: I learned to be always critical in the evaluation of complex cases. Certainly, at that time I didn't predict the extraordinary impact on diagnostic workflow of modern noninvasive imaging techniques, such as echocardiography, computed tomography (CT) and cardiac magnetic resonance imaging (CMR). Nowadays, these techniques have greatly reduced the need for autopsies in hospitals. It was during my training at the institute of pathology that, for the first time, I took my first steps toward the field of cardiology, writing my doctoral thesis on the increase in the prevalence of coronary sclerosis in the years between the Second World War and the prosperous 1960s [1].

This period was also the "Golden Age" of Zurich cardiology. I had the privilege to work with several world celebrities, such as Åke Senning, Paul Lichtlen and Andreas Grüntzig. My mentor in cardiology, Paul Lichtlen, performed the first diagnostic coronary angiography, and Åke Senning performed the first aortocoronary bypass operations in Switzerland [2–5].

The Ospedale Civico experience (1972–1999)

At the end of 1971 I was nominated head of the department of internal medicine at the Ospedale Civico, a medical division of 100 beds. With enthusiasm I started the reorganisation of this department. It must be said that at that time the hospitals in Ticino operated virtually on an "assistential" duty basis, without any technological support. I experienced the lack of modern equipment and knowledgeable collaborators. Private funding allowed purchase of the first advanced equipment. But it was in 1974 that, thanks to a donation by Helmut Horten, a wonderful German benefactor, we opened the first angiographic and haemodynam-

ic laboratory in Ticino and performed the first coronary angiographies and haemodynamic studies. Because of the lack of a cardiac surgeon in Ticino, every 2–3 weeks we discussed valvular and ischaemic patients who needed cardiac surgery with Prof. Senning, referring them to the cardiac surgery department in Zurich.

In the same period, we had the first four-bed intensive care unit, which allowed us to use defibrillator and antiarrhythmic therapy. At that time, treatment of acute myocardial infarction was restricted to ECG monitoring, defibrillation, anticoagulation and nitrates. We started to use an intra-aortic balloon pump (IABP) in cases of cardiogenic shock [6]. We noticed that mortality after acute myocardial infarction (AMI) immediately dropped from 30 to 15%.

The first Polaroid M-Mode echocardiography was essential in emergencies such as cardiac tamponade with pericardiocentesis.

In 1974, we organised a cardiobile to cover the territory. For the first time, intensive-care nurses could reach patients at home, transport them under ECG monitoring and defibrillate them when required [1] (fig. 2).

In 1978, with a young, determined and enthusiastic group of nurses, we instituted the "Scuola di Infermiere di cure intense", which later became the institutional Cantonal school.

In January 1989, we planned the first course at "la Scuola di soccorritori professionali". As mentioned, IABP was one of our primary interests. We published our experience with patients who underwent emergency coronary artery bypass graft surgery in Zurich, transported from Ticino across the Alps to Zurich by ambulance or helicopter under IABP treatment [7]. In 1973, we implanted the first pacer

Figure 2: The first cardiobile in Lugano and the Specialised Rescue School team.

Cardiobile 1974



Defibrillator + drugs
Physician and/or Intensive Care nurse

January 2nd, 1989 started the first course of the «Scuola di soccorritori professionali» of «Croce Verde»



maker – a large single-chamber system with the generator in the abdominal region. In the 1990 we implanted the first smaller dual chamber pacemakers in the pectoral region [8, 9].

In the 1980s, under the leadership of Felix Gutzwiller, we participated in three data collections in the epidemiological MONICA Trial, focused on cardiovascular risk trends in Switzerland, particularly in Canton Ticino [10, 11]. In 1975 I published several papers on coronary artery disease and cardiotoxic drugs; one of them – “Kardiotoxische Medikamente unter besonderer Berücksichtigung der Phenothiazine und Imipraminderivate” – allowed me to achieve the “Venia Legendi” at the University of Zurich [12]. In the 1970s and 1980s, I had the privilege of teaching every Friday to a group of students from Zurich University; some of them are nowadays Chiefs of various departments.

In the same years I participated as national coordinator in international multicentre trials [13]. In particular, we focused on the treatment of acute myocardial infarction with fibrinolysis, in the GISSI and ISIS trials [14–17]. Relationships with the GISSI and ISIS groups enabled us to be part of a challenging research network. We also joined several groups such as CURE, HOPE and OASIS with Salim Yusuf at Mc Master University of Hamilton, and TIMI Trials with Eugene Braunwald. With these groups we had a productive scientific collaboration.

In 1987, with Alessandro Del Bufalo I founded the “Servizio Ricerca Cardiovascolare”, a centre dedicated to multicentre randomised trials for innovative drugs. At that time, we were very impressed by the results of ISIS 2, which showed a decrease in mortality after AMI by more than 50% with use of a combination of thrombolysis and aspirin. After GISSI 1 and ISIS 2, we participated in a large number of mega trials. Notably, we published several scientific articles using the huge databases of these trials [13]. Among them I'd like to mention one focused on the behaviour of young patients with AMI in the GISSI 2 trial, published in the *Archives of Internal Medicine* [18] and one on the different outcomes of AMI based on gender, published in *The New England Journal of Medicine* [19]. In that productive period, we noticed that the combination of ECG monitoring, thrombolysis and adjunctive therapies led to a decrease in mortality after AMI of up to 8–9%.

Two Swiss cardiologists significantly changed the treatment of coronary artery disease: Andreas Grüntzig and Ulrich Sigwart. Luckily, I had the privilege to work with both of them in the 1960s in Zurich. In 1977, Grüntzig introduced percutaneous transluminal coronary angioplasty (PTCA) [20]; in 1988, Sigwart introduced the first stent in Lausanne. This latter innovation enabled effective treatment of one of the most life-threatening complications of PTCA: coronary artery dissection.

Accordingly, we began to treat patient with acute coronary syndrome (ACS) with PTCA and stent implantation, even though we had no cardiac surgery unit on site. For potential complications at that time, we had cross-border support from the cardiac surgery unit of Varese [21].

Fondazione Cardiocentro Ticino (1999)

Finally, we arrive at the last chapter of my professional life: the Cardiocentro Ticino Foundation era. Why the need of a cardiac centre with cardiac surgery in Ticino? For too many years I have witnessed of the suffering of hundreds of patients and their families, who had to cross Gottardo's tunnel, often with language barriers, hoping for adequate cardiac surgical treatment and a safe return back home. Thanks to the donation of over 40 million Swiss francs by my patient and friend Edward Zwick, a German physician, I established this nonprofit centre with a cardiac surgery department, despite strong opposition by many people including colleagues. Politicians were sceptical about building a cardiological and cardiac surgery hospital in Ticino; nevertheless, they gave permission, limiting the existence of Cardiocentro as an independent institution to 25 years, after which the Cardiocentro would be incorporated into the Ente Ospedaliero Cantonale (a multisite institution created in the 1980s). Cardiocentro was built in 16 months and started its activities on July 1st, 1999 with the first cardiac operation performed by Prof. Francesco Siclari – chief of the cardiac surgery department – a key figure in Cardiocentro. I promised to open the centre on this date during my campaign for election as Gran Consiglio, representative deputy of Lugano City. The requirement for excellent treatment of cardiovascular diseases was so urgent and widespread that, in few years, the number of employees increased from 90 to nearly 400, including 42 cardiologists and 23 fellows. During this period I had the strong support of Giovanni Pedrazzini, who shared with me this dream. Our centre is an international community with 14 nationalities. Thanks to the significant drive of my collaborators, we developed a number of different fields of cardiology.

Cardiac imaging

I am proud to say that this is one of the few worldwide institutions where all the three major imaging techniques belong to cardiology department: echocardiography, cardiac CT and CMR. Echocardiography had impressive technological improvement, from the linear scanner in 1970 to 3D echocardiography in 2010 [22]. Nowadays, echocardiography is the most-used diagnostic tool after x-ray and ECG. Transoesophageal echocardiography is essential in the operating room and as a guide in all transcatheter percutaneous procedures [23] (fig. 3). CT scan is an indispensable imaging tool to rule out coronary disease in individuals with low-to-intermediate risk of coronary artery disease, and is essential for planning transcatheter aortic valve implant (TAVI) or complex mitral valve repair. CMR in the last two decades has become a crucial noninvasive imaging modality in the cardiological workflow and it is a key for precisely defining myocardial scarring and myocardial perfusion, as well as right and left ventricular volumes and function. Having these noninvasive imaging techniques under a single direction (Dr F. F. Faletra) allows more cost-effective use avoiding redundant or overlapping examinations and correctly selecting the most effective technique for individual patients. The cardiac imaging service has published many papers in the most important journals and several books.

The radial lounge, the hydride room and interventional cardiology

In 2015, Dr Marco Moccetti created our radial lounge for patients treated via the radial approach, sometimes as outpatients. In the last 5–6 years, use of the radial approach has increased from 20 to 80%.

One of the most exciting interventions is MitraClip implantation: we performed the first procedure in Switzerland in early 2009. Currently, we are coordinating the Swiss MitraClip register.

Another source of technological support is the hybrid room – established in 2013 – where we perform structural cardiac interventions and complex arrhythmic procedures (3-chamber implantable cardioverter defibrillators, ablations) and all combined interventions, with the surgical team of Prof. Demertzis. Nowadays, using a new imaging system which fuses together echocardiography and fluoroscopy (fusion imaging), we perform almost all transcatheter percutaneous procedures for structural heart disease, including mitral and tricuspid clipping, mitral surgical-like direct annuloplasty devices (Cardioband Edwards Lifesciences, Irvine, CA, USA), occlusion of the left atrial appendage, closure of paravalvular leaks, implantation of valve-in-valve and valve-in-native valves [24] (fig. 4).

International collaborations

I would like to focus on the importance of the international collaboration network with academic centres in Europe, USA and of course Switzerland, particularly with the University of Zurich, which was implemented thank to the support of Prof. Thomas Lüscher. Since 2012 we are proud to be associated with the University of Zurich and to be a university centre; moreover, in February 2016 the FMH recognised Cardiocentro as a class-A clinical institution and training centre.

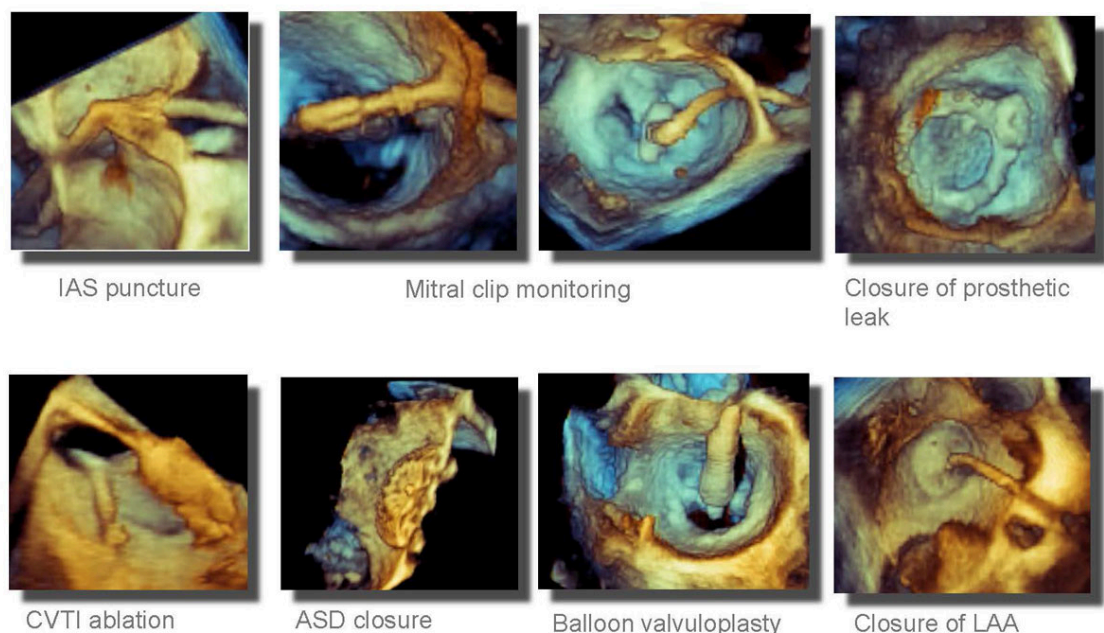
Treatment of STEMI

One of our priorities is to offer to all people in Canton Ticino, a territory bordered by the Alps in the north and by Italy in the South, the same opportunities to access high-quality cardiological treatment regardless of whether they live in peripheral valleys or more central towns. The ECG transmission project involves the transmission of ECGs from patients at home with acute coronary syndromes to Cardiocentro cardiologists via i-phone, with rescue by ambulance or helicopter (REGA). In the case of ST elevation, the secondary hospital will be by-passed. As a result, the average time between pain onset and needle could be reduced to around 60 minutes (guidelines 90 minutes). In these years we have performed more than 37 000 coronary angiographies and more than 18 000 PCIs, offering to the patients of the Canton suffering from STEMI a pain-to-needle time of 60 minutes, with the lowest mortality in Switzerland (3–4%).

Fondazione “Ticino Cuore”

Another Cardiocentro spin-off is the “Ticino Cuore” foundation for resuscitation and defibrillation of patients with sudden death in the territory. At present we have 1216 defibrillators distributed in the Canton and 84 376 people (20.3% of the Ticino population) are able to resuscitate with cardiac massage and defibrillation; more than 3000 are “first responders” after having being trained and certified in cardiac resuscitation. The collaboration with the ambulance services for a prompt transfer to our catheter laboratory for primary PCI and hypothermia managed in our Intensive Care Unit (directed by Prof. Tiziano Cassina) resulted in an increase in survival from 15% (the Swiss average) to 50%. With the help of the University of Applied Sciences (SUPSI), an app to geo-localise the patient, the nearest defibrillator and first responder has been developed, permitting a further decrease of mortality [25]. This capillary organisation across the territory has given a general sense of protection (fig. 5).

Figure 3: 3D imaging of different percutaneous procedures.



Servizio Ricerca Cardiovascolare

Another activity of Cardiocentro I am proud of is the “Servizio Ricerca Cardiovascolare”, active since 1987, and currently employing 12 collaborators (all women) lead by

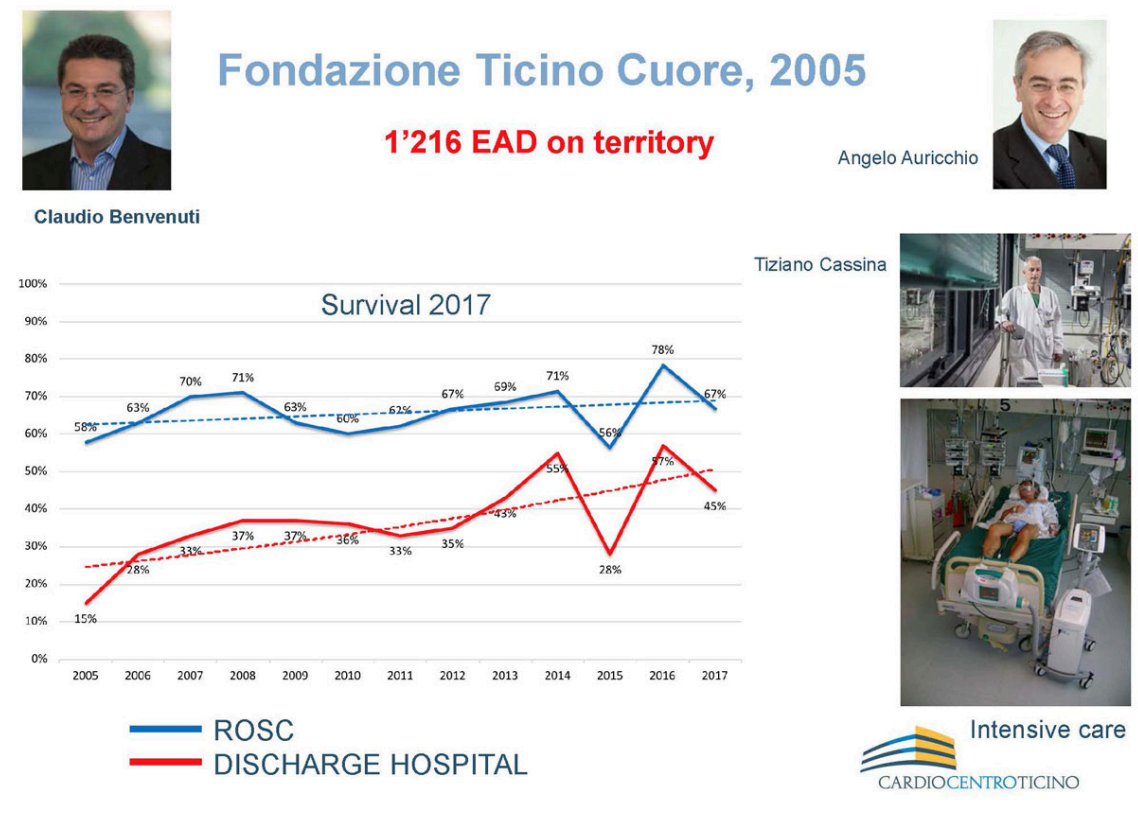
Dr. Elena Pasotti and Dr. Mariagrazia Rossi. We follow up on many randomised clinical pharmacological and device trials in various research areas, with very skilled and dedicated nurses. At the moment we are involved in 53

Figure 4: Interventional cardiology team.



Figure 4: Cardiology Interventional Team

Figure 5: Follow-up of outcome according to Utstein criteria.



trials or registers (on-going and follow up), with more than 1400 patients monitored yearly. A typical example in which we were extensively involved was the evaluation of new antithrombotic drugs, such as TRITON with prasugrel, PLATO with ticagrelor and OASIS-7 with double-dose clopidogrel. In all of these trials we have been a high randomising centre. More recently, the new trials with anti-PCSK9 antibodies resulting in a huge decrease in cholesterol levels (FOURIER, ODYSSEY) and a significant decrease of cardiovascular events.

Electrophysiology and Centre for Computational Medicine in Cardiology

In cardiac electrophysiology, the Cardiocentro team implants a large number of pacemakers (~6000), ICDs, cardiac resynchronisation devices (CRTs; ~1500). Angelo Auricchio was the first electrophysiologist in the world to implant the first wireless pacemaker. The electrophysiology service has published many papers in the most important journals and several books [26, 27]. One of the latest spin-offs of Cardiocentro is the Centre for Computational Medicine in Cardiology, where Prof. Angelo Auricchio and Prof. Rolf Krause of US, are developing virtual cardiac models using the ETH super computer in Lugano [28].

Translational cardiovascular medicine and SIRM

In the field of translational cardiovascular medicine, we were the first in Switzerland to perform intracoronary injection of bone marrow stem cells in 2004 [29]. This study followed the protocol used in the REPAIR trial of Andreas Zeiher's group. In 2010, the Cardiocentro created the first GMP cell factory approved by Swissmedic, which employ seven collaborators. One important study in cellular therapy is the Swiss AMI trial [30], for which we processed stem cells for all involved institutions: the study compared early vs late infusion of bone marrow stem cells after AMI, with the randomisation of over 200 patients. Unfortunately, the results were not significant.

A further spin-off of Cardiocentro is the Foundation for Cardiovascular Research and Education (FCRE), mostly financed from Cardiocentro. To the question "which is the best cell?" we developed the SIRM (Swiss Institute of Regenerative Medicine) laboratory – located a few kilometres from Cardiocentro – where Prof. Giuseppe Vassalli, Lucio Barile and 43 collaborators work on regenerative medicine, in particular using exosomes that appears to provide cardioprotection in animal models of AMI [31]. As the only Swiss Centre, Cardiocentro and SIRM participate in the European BAMI trial of stem cell therapy after acute myocardial infarction, and in the international CHART-1 (Clinical Trial about Heart Failure Cardiopoietic Regenerative Therapy) [32].

In our project on the final stages of heart failure we occasionally use ventricular assist devices (VADs) for destination therapy. One patient, unsuitable for heart transplantation, underwent VAD implantation in January 2011, thanks to a donation by the Fidnam Foundation. Seven years after the implantation, he still has an active lifestyle.

Meetings and humanitarian projects

Thanks to the active participation of our collaborators in major international meetings, we are up-to-date on devices

and drug therapy, and, more importantly, we maintain human relationships with international colleagues to develop the best treatment for our patients. We have also organised several international meetings, nine MTE ("Meet The Expert") with cardiac interventional live cases, five SCM ("Stem Cell Meeting") in regenerative medicine [33], and some of the last TRM Forums ("Theo Rossi di Montelera") organised by Prof. Kappenberger on innovative electrophysiology. Participants could consider a large number of live cases involving PTCA, surgical interventions, mitral valve implantations, TAVI and other interventions.

An important annual event is the Cavaliere del Cuore meeting, at which cardiac arrest survivors are able to thank those who helped them with resuscitation: a really emotional moment.

We also collaborate in humanitarian projects for cardiopathic children with "Fondazione Bambini Cardiopatici nel mondo", founded in 1999. We participated in the "SIRIA 2000 project", a paediatric surgery institute in Damascus, where, despite the war, the team could perform 337 cardiac interventions on children in 2017.

We were involved with the "Guinea Bissau project" in which 22 compassionate interventions were performed in Cardiocentro; for the future we will sponsor 50 cardiac interventions on site every year at "Ospedale Cuomo" in Dakar (Senegal). Some of our collaborators visit the hospital in Guinea Bissau twice a year; a recent study showed a prevalence of rheumatic valvular heart disease of 8% in 2441 children visited.

The current Cardiocentro situation

Finally, let me focus on the current Cardiocentro situation: Will the institution remain a nonprofit foundation after 2020 or will it be incorporated into the public Ente Ospedaliero Cantonale? My only hope is that the quality of Cardiocentro, developed over all these years, can be maintained.

Our future (fig. 6), to some extent already ongoing, has a main focus on valvular interventions and, of course, personalised cardiology, genetics and new drugs. One of our priorities is our participation in the new Medicine Master in Biomedical Sciences of the Swiss Italian University (USI) in Lugano, where Prof. Pedrazzini, my co-chief, is the elected full professor of cardiology.

I cannot forget one special day, organised by myself and Aldo Maggioni: a vision of the future of past projects, discussed in 2016 by a group of friends in Cardiocentro, with one World Heart Federation President (Salim Yusuf), two European Society of Cardiology Presidents (Roberto Ferrari and Barbara Casadei) and some legends in cardiology (Mark Pfeffer, Rory Collins, Richard Peto, Gianni Tognoni, Attilio Maseri and others). Recently a Separatum in the European Hear Journal has been published with the title "Lugano Perspectives" in cardiovascular diseases [12, 34].

To conclude, let me mention the "Mizar", a building located downtown in Lugano, which represents the new dream of Cardiocentro Ticino in collaboration with the Municipality of Lugano and the Swiss Italian University for basic and translational research, an open bet.

Figure 6: My dream: Lugano perspectives.

All of this long journey was possible thanks to the support of all collaborators, and to the trust of the foundation council and of the Administrative Direction of Cardiocentro. But most of all I have to thank my parents, my wife Laura, my three sons and my nine grandchildren. They have been present not only in the happy moments of my life, but especially through the difficulties.

I want to close by quoting Darwin: “It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to the change.”

My particular thank goes to the Swiss Cardiology Society for the Andreas Grüntzig Lecture. I am proud to accept this honour for the Cardiocentro Ticino team and for the Ticino population.

The literature references came from 525 publications (peer and not peer reviewed papers) collected between 1996 and October 2018.

Disclosure statement

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