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Building on the shoulders of giants: the Valve Academic Research Consortium (VARC) initiative towards a global framework to guide valvular heart disease trials

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In April 2006 EuroIntervention published the very first of its special supplements based in part on the then ground-breaking Transcatheter Valve Symposium (TVS). This Supplement was guest edited by the two directors of the Symposium, and pioneers in valve treatment and education themselves, Philipp Bonhoeffer and Carlos Ruiz. The work of this first Supplement, as many of the following as well, was aided by the distinctive and important contributions made by the Supplements editors Alec Vahanian and Pieter Kappetein.

In our own lives a little more than six years is not a very long time, but for the percutaneous treatment of valve disease it is enormous. Today, what was an experimental idea has developed into a mainstream clinical practice accepted and practiced worldwide, and the time has clearly come again for another supplement, this time as an integral part of what has become our dedicated valve meeting, PCR London Valves. Again, our guest editors for this Supplement are the Course directors themselves, Martyn Thomas and Stephan Windecker.

The rapid evolution in percutaneous valve technologies could not have come about without the structure and foundation that was laid at the very beginning, even before what could now be called the percutaneous valve replacement era. TAVI has certainly been built on the shoulders of many giants whose commitment to an idea, and historic understanding of technique and technologies, allowed them to progress. While we frequently hear mentioned the exacting and ground-breaking work of Phillip Bonheoffer and Alain Cribier on the clinical side, we should also add to this particular pantheon the early efforts of Henning Rud Andersen, the Danish interventional cardiologist whose own pioneering work with pigs hearts laid one of the foundations – as well as an early publication – concerning the feasibility of replacing valves percutaneously.

In 1991 Henning Rud Andersen obtained a patent on his early development of an experimental porcine valve. Writing up these experiences, he reported the results of implanting his device in nine pigs, an article which was not accepted by any of the scientific journals of the time until I reviewed the paper. Immediately seeing that this approach could solve the problem of early valvular restenosis, a problem we had been observing following balloon valvuloplasty in aortic stenosis, I recommended publication[1]. As I learned later, through all the disbelief that followed his research, Henning Rud Andersen remained positive, saying today, "My message to young cardiologists is that if you've an idea you truly believe in you should be prepared to fight and never give up." Recently his father successfully received TAVI, a remarkable and direct result of his son's pioneering spirit.

Still the mere commitment of doctors to an idea is not enough. After the initial inspiration, and undeniable acts of clinical courage, a scientific framework is necessary for an idea to become a discipline. A foundation is composed of just this, and in seeking the proper structure, we developed the VARC, the Valve Academic Research Consortium as a sort of sounding board by which the advancement of valvular technologies could be judged and implemented.

In 2009, in an early editorial in EuroIntervention by Nicolo Piazza and myself, we spoke about how we were puzzled that the pioneers in the implementation of TAVI were publishing studies "characterised by a great deal of heterogeneity involving the definition of clinical endpoints."[2] We felt that many were expressing a desire concerning "the need for standardising reporting practices". An example of this desire was illustrated the year before, in 2008, when EuroIntervention published a position paper on TAVI

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in patients with aortic stenosis (AS) by Alec Vahanian et al for the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). In our editorial we went on to challenge the community at large, asking if we had "achieved a sufficient level of understanding of the benefits and risks associated with TAVI to begin discussions on the standardisation of clinical-endpoints?" In line with the then developing concept of the "Heart Team" as well as an across-the-board commitment to an interaction by all players in the field, we said that it was "…time for a collaborative effort among interventional cardiologists, cardiac surgeons, regulatory bodies, and device manufacturers and that just such a consortium would provide the initial momentum to guide us in the right direction. The need for randomised controlled trials to adequately assess the outcomes of TAVI demands standardised definitions and the involvement of central core laboratories will be essential in their implementation.". We ended our editorial with a call to arms: "Let us not make the same mistake as in stent trials – This editorial is a call for a Valvular Academic Research Consortium (VARC)."

And so the VARC was born, with the original VARC document being published in January of 2011. The first consensus manuscript[3,4] concentrated on two points: first, the selection of appropriate clinical endpoints reflecting device, procedure and patient-related effectiveness and, secondly, safety and the standardisation of definitions for single and composite clinical endpoints for TAVI clinical trials.

The VARC came out of the combined input of all the participants, and represented a truly international effort. The upcoming VARC 2 reflects this as well and is the result of academic research organisations: Cardialysis (Rotterdam, The Netherlands); Cardiovascular Research Foundation (New York, NY, USA); Duke Clinical Research Institute (Durham, NC, USA) and Harvard Clinical Research Institute (Boston, MA, USA). It includes learned professional societies from the US and Europe such as the American College of Cardiology (ACC) with David Holmes, the European Association for Cardio-Thoracic Surgery (EACTS), the European Society of Cardiology (ESC) and the Society of Thoracic Surgeons (STS). Members of the US Food and Drug Administration (FDA) were actively involved as were representatives from industry.

A recently published pooled analysis which included 3,519 patients from 16 unique studies confirmed that the earlier VARC definitions have already been incorporated into clinical and research practice, and that these "represent a new standard for consistency in reporting clinical outcomes of patients with symptomatic severe aortic stenosis (AS) undergoing TAVI[6]."

Still, it had become increasingly clear as TAVI expanded that the breadth of the earlier VARC needed to be enlarged and adapted to emerging data. Our clinical experience with this technology has rapidly matured and its use has expanded. Definitions, for instance, concerning risk scores and comorbidities, appeared to be inaccurate contributing to the lack of certain clinical and anatomical variables on which the mortality-estimate is based (porcelain aorta, frailty, etc.). The aim of VARC 2 is thus to "re-examine the selection and definitions of TAVI-related clinical endpoints to make them more suited to present and future practice and trials". Additionally, VARC 2 is intended to expand understanding of patient risk stratification and selection. As we did in the earlier VARC 1 process, two in-person meetings were held in September 2011 in Washington, DC, USA, and February 2012 in Rotterdam, The Netherlands which involved the VARC study group members described above. From these "substantive discussions" the VARC 2 consensus emerged, with a new manuscript to be published shortly in four different journals[7].

The VARC process, like the ARC before it, and other initiatives such as the Blood Academic Research Consortium (BARC) are essential for the orderly development of our practice. These, joined with our increasing integration of the Heart Team and multidisciplinary studies and practices will continue to strengthen the foundation of those who went before us. These foundations are strong, but they are only of use if we can build a competent and supple structure upon them that will withstand the winds of change, adapting to the evolution of our knowledge and our ability to achieve consensus and communicate our knowledge effectively. The Academic Research Consortiums are just such a mechanism and the VARC initiative and process – with its upcoming second publication – is an excellent, essential and necessary example of this.

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