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EDITORIAL

Long Term Evaluation Should Be an Integral Part of the Clinical Implementation of New Vascular Treatments - an ESVS Executive Committee Position Statement

Innovation is the driving force for improving results after vascular procedures: prior achievements led to the endovascular revolution, dramatically changing today's vascular practice and enabling specialists to treat patients more safely, with lower morbidity and short term mortality.

We are naturally interested in treating patients in the best possible way, not just as efficiently as possible, but also by critically and continuously improving patient care. Courage and humility are essential: both attitudes must be balanced when evaluating promising new techniques or products with potentially exciting benefits. Successful pioneers are rewarded by publications in high impact factor journals, appreciation from sponsoring companies, and gratitude from their patients. New techniques may sometimes be adopted quickly into clinical practice, driven by ingenious designs and successful preliminary reports. This can lead to widespread distribution and early agreements to reimbursement. Legislation differs around the world. Introduction of new medical devices to the market has until recently generally been easier in Europe than in the United States or Japan, resulting in earlier introduction of several new techniques and products on the European market, often after only relatively small and short observational studies. This seems astonishing if you look back at the last 30 years of vascular device invention: almost every make of first generation endovascular aortic repair (EVAR) grafts were explanted due to long term failures.[1]

Shorter hospital stay and lower peri-procedural morbidity are important early benefits of innovative techniques or new products. As patients appear to benefit, these advantages are highlighted by surgeons and manufacturers. Sometimes patients ask for these new techniques and urge us to use the newest and most promising treatment available long before benefits are proven or long term results are available.

Compared with plain balloon angioplasty and bare metal stents, drug coated percutaneous transluminal angioplasty (PTA) balloons and stents may indeed offer benefits to patients, with better freedom from target lesion revascularisation and longer patency, supposedly without serious consequences.[2] However, recent, worrying results from a meta-analysis on long term mortality from these devices have disturbed the vascular community, raising concerns about accreditation of new devices.[3] Conflicting messages from regulatory bodies (US Food and Drug Administration) have been released, because available data were insufficient to give clear answers.[4]

How sound are these data before new practices are introduced? Current important non-commercial clinical trials have been temporarily paused showing that there is a clear need for reliable research, especially into long term outcomes.[5,6] Additionally, just before the current paclitaxel issue in peripheral vascular angioplasty, the Nellix (endovascular aneurysm sealing, EVAS) device for aortic aneurysm sealing was recalled following reports about serious failures, despite promising early post-market results.[7] By the time they were withdrawn, both EVAS and drug coated peripheral devices had been widely used by physicians, based on limited long term outcome data.

As physicians and clinical researchers, it is our responsibility to assess reliable long term outcomes before exposing our patients to new devices and techniques. Outcomes should be based on unbiased, well powered randomised clinical trials, long term safety studies and real world practice. Device and pharmaceutical companies play a major role here, there is real mutual interest in new evidence. But bias still exist for industry and researchers: intervention trials are often industry sponsored and trial design data monitoring and stopping rules may still be subject to interference, as well as disputes on ownership of data.

Innovation needs long term proof of safety for devices and drugs. It may not be ethical to stop a trial early, only because early benefit appears "proven" (it might be, with longer follow up and more patients, that the trial shows no benefit, or even harm?).[8] How do we protect our patients from potentially harmful innovations, while still encouraging research? Certainly, benefits from innovations should be made available as early as possible, with prompt investigation and close follow up in properly conducted, unbiased prospective trials and long term follow up in registries and trials. We also need international clinical trial centres, with clinical trial leaders, approved safety monitoring and good clinical practice (GCP) certification to achieve sound and well proven data.

Funding should be independent. International healthcare policies should be harmonised to achieve best possible medical care: this may play a central role in the future of clinical research. This will require each country to sign up to

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trusting other partner countries to participate in an honest and reproducible study. Clinical trial purpose, design, size, and outcome values need independent evaluation. Clinical trial centres may be unbiased, but they will also need a thorough knowledge of the field of research and of the clinical environment and purpose for conducting any proposed trial, as well as an appreciation of the healthcare economics for the whole partnership. The European Union has now introduced new medical device rules (EU-MDR), which come into force on 27 May 2020, following a three year transition period. These rules aim to increase patient safety, *ex ante* control for high risk devices, criteria for notified bodies, risk classification system for *in vitro* diagnostic medical devices, improved transparency, "implant card" (unique device identification [UDI]). Additionally, rules on clinical evidence and coordination mechanisms have been introduced. The need for lifelong product evaluation of all medical devices is fully in line with the points discussed in this Editorial. However, the new EU-MDR might place European vascular surgeons in the back seat in terms of innovation and progress of vascular surgery, should companies choose to prioritise other markets with a lower regulatory threshold for introduction of new techniques. Therefore, there is a global need for balanced and appropriate measures to enable the safe introduction of new treatments to the European market in line with new regulations, to achieve the best patient care worldwide. The European Society for Vascular Surgery (ESVS) and vascular surgeons in Europe will have a clear leading role here.

Post-market surveillance is mandatory to assure long term safety. Device registries have been introduced to achieve this. Strict regulatory rules may lead to a reduced number of innovations reaching the market; however, improved safety should also be achieved. Manufacturers are now responsible for generating future post-market data. Any discussion on randomised clinical trials generating insufficient evidence *vs.* improving registry based research with its focus on "real world evidence" will probably continue. Real world evidence from registries is an important adjunct to meaningful randomised clinical trial research, where external and internal validation plays a major role. Although we may not be able to prevent long term failures in medical devices or innovative techniques, we can do our best to ensure that failures are detected as early as possible — before widespread clinical use.

What is the role of vascular surgeons in all this? First, we have to realise that there would be no product failures had we not used the failing devices. We should be critical when exposed to new products. Is there a need for it and is there good evidence behind the introduction (clinical data)? However, we are aware that for numerous reasons there will never be randomised controlled trials and long term clinical data for all new products when introduced to the market. A way forward for the vascular surgeon under these circumstances would be to use new products only where the manufacturer provides a sound international registry where all use is entered, followed, and continuously evaluated by third party authority.

Before concluding, let us have a close look at the recent report of long term data from the Veteran Affairs Open Versus Endovascular Repair (OVER) trial. At median follow up of 9.4 years (interquartile range 5.7—11.2 years), there was no difference in the primary outcome of all cause mortality between patients with an asymptomatic abdominal aortic aneurysm treated by EVAR or open repair (OR), but more patients in the EVAR group underwent secondary procedures.[9] Interestingly, during the first four years of follow up, overall survival appeared to be higher with EVAR than OR; from year four to year eight, overall survival was higher in the OR group; and after eight years, overall survival was once again higher in the EVAR group. Although none of these trends were significant, this emphasises the importance of extended follow up of these patients in whom procedures were performed more than a decade ago.

The leadership of the ESVS and the editors of the *European Journal of Vascular and Endovascular Surgery* (EJVES) strongly encourage the conduct of high quality studies reporting long term follow up. Only with this objective in mind will we continue to deliver the best possible care to our patients.[10]

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Henrik Sillesen
Department of Vascular Surgery, Rigshospitalet, Denmark
Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Sebastian Debus
Department for Vascular Medicine, University Heart and Vascular Centre, Hamburg, Germany

Florian Dick
Department of Vascular Surgery, Canton Hospital St Gallen, St Gallen, Switzerland
University of Bern, Bern, Switzerland

Jonas Eiberg
Department of Vascular Surgery, Rigshospitalet, Denmark
Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
Copenhagen Academy for Medical Education and Simulation (CAMES), Rigshospitalet, Denmark

Alison Halliday
Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

Stephan Haulon
Aortic Centre, Hôpital Marie Lannelongue, INSERM UMR_S 999, Université Paris Sud, Paris, France

Vincent Jongkind
Department of Vascular Surgery, Dijklander Hospital, Hoorn, the Netherlands

Hence Verhagen
Department of Vascular Surgery, Erasmus University Medical Centre, Rotterdam, the Netherlands

Pirkka Vikatmaa
Department of Vascular Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Philippe Kolh*
Department of Biomedical and Preclinical Sciences, University of Liège, Belgium

*Corresponding author. Department of Biomedical and Preclinical Sciences, University of Liège, Sart Tilman B 35, 4000 Liege, Belgium.
Email-address: philippe.kolh@chuliege.be (Philippe Kolh)