Neuroradiology (2010) 52:653–654
DOI 10.1007/s00234-010-0706-5

TOPIC ARTICLE

Individual off-label use needs to be replaced by controlled studies

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Received: 26 March 2010 / Accepted: 12 April 2010 / Published online: 26 May 2010

In the current issue of *Neuroradiology*, Hans Henkes and colleagues present a case series of 40 patients with intracranial stenoses who received endovascular treatment with off-label use of a flexible coronary stent. The interventions were performed after informed patient consent on the basis of an individual therapeutic decision in a defined clinical setting; however, the interventions took place outside of any predefined study protocol. What is more, stent manufacturers have yet to design products for the indication intracranial atherosclerosis.

Above and beyond the fact that the authors do not follow common rules of testing new techniques or medical devices [1, 2], their proceedings reflect an important part of the neurointerventional business in Europe and should be discussed.

The process of CE approval primarily focuses on technical function tests or experimental data and does not necessarily demand clinical studies under controlled conditions with a predefined protocol or approval of an ethics committee. Some neurointerventional devices, especially stents, have received a CE mark without clinical study if the catheters and implants are technically similar to existing products and if a notified body is convinced that it should work. Such liberal approval procedures open the European market for clinical testing of new and innovative techniques without the restrictions given by sometimes bureaucratic and expensive regulations of the FDA approval in the USA.

However, despite the benefits of liberal approval procedures, trust in the value of CE approval is limited, and the threshold for off-label use is low. In the case of rare diseases such as intracranial stenoses or giant aneurysms, we are faced with approval authorities and device manufacturers who are typically reluctant to enter into controlled approval processes that include a minimum of clinical data about technical feasibility and safety.

In essence, the difference between off-label use or use of CE marked products without clinical approval study is too low to encourage manufacturers to undergo this process, and yet, the practice of CE marking without clinical data has led to questionable, frequently commercially biased post-marketing studies.

Apart from reasonable scientific regulations, clinical testing of new devices or available materials for new indications is frequently done in a parallel world of high volume interventional centers. Thus, patients may be treated with the use of devices with unknown or unpublished clinical success and complication rates. The advantage of the work of Henkes and colleagues is that they have published their results and created a forum for discussion.

Nonetheless, we have to ask whether the approach of a pioneer interventionalist who tries new techniques on his own initiative on the basis of individualized therapy is adequate for a large case series. At the current stage of development, interventional neuroradiology is increasingly confronted with demands to prove the effectiveness of procedures by means of controlled clinical trials. In

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addition to technical approaches, a minimum of formal criteria, study protocol with defined study population, inclusion criteria, endpoints, and follow-up schedule, approval of an ethics committee and informed consent of the patient about the participation on a clinical study are required as prerequisite for the introduction of new techniques to get first reliable feasibility and safety data.

In short, we should prefer materials that have been tested or are still investigated in controlled multi-center trials or registries (even if company funded). We need to improve the culture of investigator-initiated trials on interventional neuroradiology materials. Positive examples have already paved the way [3].

Conflict of interest statement We declare that we have no conflict of interest.

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