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Clinical studies of innovative medical devices: what level of evidence for hospital-based health technology assessment?

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Abstract

Rationale, aims and objectives Like health technology assessment (HTA) agencies, hospitals are faced with requests for innovative and costly medical devices. However, local decision makers are frequently confronted with a lack of high-quality clinical data when assessing the effectiveness of innovative medical devices. The aim of this study was to quantify the level of evidence available for innovative medical devices in the context of hospital-based HTA.

Methods We searched the Medline, Embase and Cochrane Library databases for articles, letters and reports relating to 32 innovative medical devices requested at our hospital between January 2008 and March 2012. All clinical studies retrieved were screened and classified according to the Sackett 5-point level-of-evidence scale.

Results We screened and classified 217 studies: 215 clinical trials and 2 cost-effectiveness studies. Only 47 of the 215 clinical studies (22%) provided high-level clinical evidence (levels 1–2); 33 (15%) were randomized controlled trials (RCTs). More than half of the 215 studies (52.1%) included fewer than 30 patients. Only 14 of the 47 high-quality studies reported the amount of missing data. For implantable medical devices, 84 (71.8%) studies specified the follow-up period and the mean follow-up period was 18.9 months. Finally, methodological quality did not increase with the risk level of the medical device.

Conclusions Our findings confirm that only a few studies of innovative medical devices provide high-level clinical evidence. Nevertheless, RCT may be the 'gold standard' for drugs, but it is not always appropriate for medical devices. Changes to the European regulation of medical devices, with the requirement for a demonstration of clinical efficacy and safety before release onto the European market, have raised expectations.

Introduction

Medical devices are essential for the prevention, diagnosis, and treatment of illness and disease, but can also improve the quality and safety of care. The complexity of these medical products varies greatly from medical aids, such as gloves or wound-care products, to implantable devices, such as pacemakers. In the European Union (EU), medical devices are regulated by three EU directives: 90/385/EEC, 93/42/EEC and 98/8/EC. For market release, a medical device must receive European Conformity (CE) marking from a Notified Body, indicating that it is licensed for use within the EU. This requires the manufacturer of the medical device to demonstrate that the safety and performance of the product comply with the legal requirements laid down in the EU directives and to submit a definition of its intended use. There are four classes of products – classes I, IIa, IIb and III – ranked in ascending order of risk. Thus, higher class numbers are associated with a greater level of assessment. Until recently, EU directives did not require clinical data relating to medical effectiveness for medical devices. Since March 2010, the introduction of a new directive (2007/47/EC) has made such data mandatory for high-risk devices (class III) [1]. Manufacturers must now carry out clinical investigations in humans or produce a comparative literature review demonstrating that the device is similar to an existing product with CE marking [2]. However, this new directive does not specify the depth and extent of clinical trials required. Even specific guidelines, such as European Commission MEDDEV 2.7/4 from December 2010, provide no clear rules concerning the way that effectiveness should be evaluated [3]. Thus, most medical devices are currently released onto the EU market without high-quality data [4].

Many European countries have implemented formal policies promoting the development of health technology assessment (HTA) to improve the uptake of new technologies [5]. HTA can be

defined as a multidisciplinary field involving studies of the medical, social, ethical and economic implications of the development, diffusion, and use of health technology [6]. HTA is increasingly being used by health care organizations to support evidence-based decision making and to prevent the uptake of technologies that are of dubious value. In most European countries, HTA activities are generally the responsibility of a national agency for HTA, but these activities have increasingly been decentralized in recent years. Following the same principles as 'classical HTA', hospital-based HTA has been developed to help hospital management deal with technology acquisition issues [7,8].

Both nationally and locally, decision makers need high-quality information about the clinical efficacy/effectiveness of medical devices to support their decisions. The health authorities of each EU member state have established additional regulations for the national coverage of medical devices [9]. These HTA agencies frequently require supplementary data on efficacy/effectiveness from post-market release studies to support their decisions. This is somewhat paradoxical because such assessments become available to the decision makers only after the medical device has been adopted in practice and is widely used. Thus, hospitals are often faced with demands for innovative medical devices that are not always covered by the health authorities and for which few clinical data are available. So what quality of clinical data do hospitals use to guide their decisions concerning the introduction of innovative medical devices? The aim of this work was to analyze, retrospectively, the requests made by surgeons and clinicians for all innovative medical devices over a 4-year period in a French university hospital, reviewing all the clinical data available at the time of the request and ranking the studies in terms of the quality of evidence provided.

Materials and methods

Doctors wishing to introduce a medical device that is not already referenced in the hospital must submit a written request to hospital pharmacists. The doctor must justify the request by completing a form and the hospital pharmacists carry out a limited literature review to evaluate the efficacy/effectiveness of the medical device. Some of these requests may concern innovative or costly devices. We used the definition provided by the EuroScan International Network to determine which devices could be considered innovative: 'emerging technologies are technologies that are not yet adopted by the health care system. [. . .] Medical devices will be prior to marketing, or within 6 months of marketing, or marketed but less than 10% diffused or localised to a few centres'.

Search strategy

We selected all requests for innovative medical devices, as defined by the EuroScan International Network, between January 2008 and March 2012 to assess the level of evidence provided by clinical data. For all these requests and for each indication, we defined keywords and conducted a literature review based on three medical databases: the Medline, Embase and Cochrane Library. This literature review was conducted in April 2012. For each medical device, we searched for studies including the brand and generic names of the device. Various combinations of terms were used due to the wide range of denominations used for the same device. The aim of this work was to assess the level of evidence available from clinical studies at the time of the request for an innovative medical device. Thus, for each database search, the date at which the doctor's request was made was entered as a deadline.

Table 1 Levels of evidence of clinical studies

Evidence level	Characteristics of the clinical study
1	Prospective randomized controlled
2	Prospective non-randomized controlled
3	Prospective
4	Retrospective
5	Case report

Selection of relevant articles

We included articles, letters and reports published in English and French. We did not explore the 'gray' literature constituted by organization web sites and papers from conferences. For all selected articles, we tried to retrieve the full published report. It this proved impossible, we restricted our analysis to the abstract. However, abstracts were not informative enough for all analyses and were therefore excluded from some.

Data abstraction

We noted the methodological characteristics of each clinical study by determining whether the study was prospective or retrospective, controlled, randomized, single or multicentre; the number of patients; the design of the study (open, single or double blind); whether there was a single primary outcome; and the reporting of statistical analysis, sample size calculation and follow-up periods for implantable medical devices. We then classified the clinical studies according to their level of evidence, as established by Sackett *et al*. Levels of evidence are summarized in Table 1 in descending order. The Sackett level-of-evidence scale has been used in other similar studies of medical devices [10].

Clinical studies with a level of evidence of 1 or 2 were classified as having high-quality data, whereas clinical studies with a level of evidence of 3, 4 or 5 were considered to have poor-quality data.

Results

Description of innovative medical devices

In total, there were 32 requests for innovative medical devices between January 2008 and March 2012. The cardiovascular field was the most frequently represented among the selected requests (Fig. 1). Overall, 28 (87.5%) of the 32 innovative medical devices belonged to the high-risk classes (IIb and III) and 21 (65.6%) were implantable devices (Table 2).

Description of the literature review

The electronic search yielded 217 articles: 215 clinical studies and two cost-effectiveness studies. There was therefore a mean of 6.8 studies per innovative medical device. Nevertheless, the number of

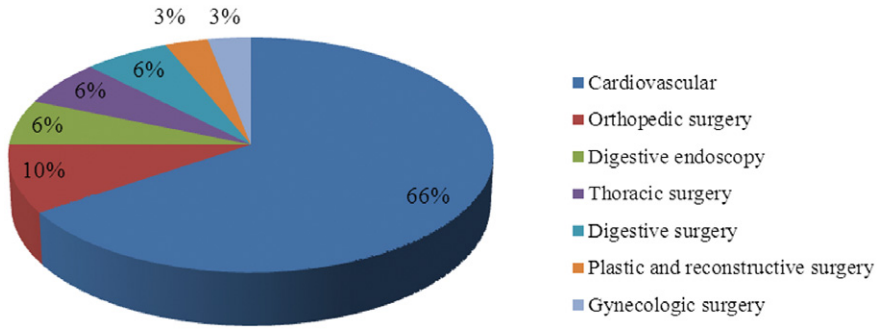

Figure 1 Distribution, by specialty, of requests for innovative medical devices.

Table 2 Characteristics of medical devices

CE marking classification	Number of innovative medical devices	Number of implantable medical devices
I	2	0
IIa	2	0
IIb	6	5
III	22	16

CE, European Conformity.

Table 3 Number of clinical studies per class of the CE marking classification

CE marking classification	Number of innovative medical devices for which no clinical data are available	Number of clinical studies ($n = 215$)
I	0	16
IIa	0	18
IIb	2	28
III	4	153

CE, European Conformity.

studies per device was highly variable, with no clinical data available for 6 medical devices and 38 clinical studies on another device (Table 3). The full text was available for 187 articles. For the analyses of missing data and follow-up periods for implantable devices, we took into account only the articles for which the full text was available.

Analysis of the methodological quality of the clinical studies

Only 47 clinical studies (22%) had high-quality data (Fig. 2). Most (81.3%) of the studies relating to class I medical devices had high-quality data. However, this was not the case for the other classes of medical devices. Indeed, only 5 (17.9%) clinical studies relating to class IIb devices had high-quality data: 2 prospective randomized controlled studies and 3 prospective non-randomized comparative studies. Seventeen studies were purely prospective, one was retrospective and five were case reports. For class III medical devices, the data were of high quality in 27 studies (17.6%): 27 prospective randomized controlled studies and 126 prospective non-randomized comparative studies. Fifty-three studies were purely prospective, 35 were retrospective and 38 were case reports. Only 29.8% of the studies with high-quality data were multicentre studies.

Thus, the methodological quality of the studies did not increase with the risk level associated with the medical device. The mean number of patients in the clinical studies retained for this analysis was 83.7, but more than half of the studies (52.1%) included fewer than 30 patients.

Blinding status was reported for the 33 randomized controlled studies. Twenty-three of the clinical studies (69.7%) were conducted in an open-label condition. Only 8 studies (24.2%), all relating to class III medical devices, were double blind.

We also focused on articles reporting the sample size calculation. This calculation is designed to determine the number of patients required for assessments of the safety and effectiveness of the device. It must be reported and justified in published articles to facilitate evaluation of the methodology of the study. Only 39.1% of the studies with high-quality data reported sample size calculation. The calculation of sample size in clinical studies is based on primary outcome. It is therefore important to define a single primary outcome and any secondary outcome measures clearly in the study protocol. We found that 29.4% of the prospective randomized controlled studies and 88.9% of the prospective non-randomized comparative studies had more than one primary outcome or no primary outcome.

Many randomized controlled studies suffer from the problem of missing data. These missing data can bias the results and cause a

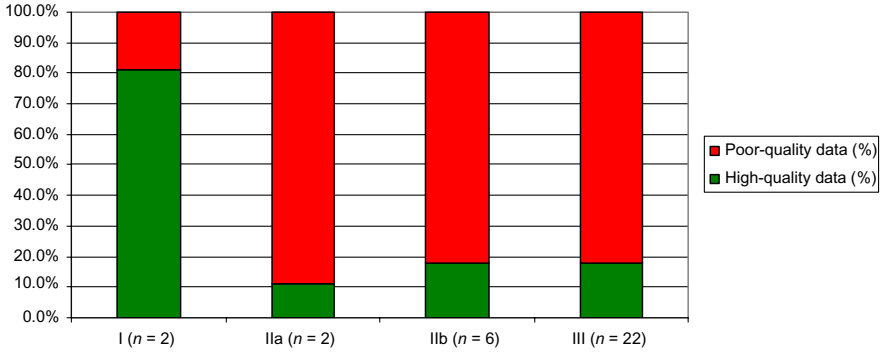

Figure 2 Level of evidence in clinical studies by clinical evidence marking classification.

Table 4 Level of added clinical value according to the CNEDIMTS

Level of added clinical value	Degree of improvement
I	Major improvement
II	Substantial improvement
III	Moderate improvement
IV	Minor improvement
V	No improvement

CNEDIMTS, National Committee for the Evaluation of Medical Devices and Health Technologies in France.

loss of statistical power and precision. Thus, the handling of attrition must be described in published articles for a correct understanding of the results. The full text was available for 46 of the 47 studies with high-quality data, but only 14 (30.4%) reported the amount of missing data and the method used to handle missing data in the analyses.

The follow-up periods were reported for implantable medical devices. The full text of the article was available for 117 studies, 84 (71.8%) of which specified the follow-up period, the mean follow-up period being 18.9 months.

In France, the French National Authority for Health (*Haute Autorité de Santé*) and its medical devices committee (National Committee for the Evaluation of Medical Devices and Health Technologies; *Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé*; *CNEDiMTS*) evaluate clinical data for implantable devices to guide decisions concerning national reimbursement. The members of the CNEDiMTS base their scientific assessment on the clinical data available. The actual benefit of the device for a given indication is adjudged insufficient or sufficient for reimbursement. If the actual benefit is considered sufficient for reimbursement, the CNEDiMTS assesses added clinical value with respect to the reference strategy, or the strategy used in routine practice in the absence of scientific evidence (Table 4).

Ten of the 21 implantable devices studied were found to have sufficient actual benefit for reimbursement via the French social security system. The added clinical value was qualified as 'substantial' for one device (a phrenic nerve stimulator) and 'minor' for another (implantable cardiac stimulator compatible with magnetic resonance imaging), whereas the other eight devices were considered to be of no added clinical value.

Discussion

Principal findings

As stated above, the CE marking concerns only the safety and performance of a device. Thus, many medical devices come onto the market with data from only a few clinical studies. Moreover, the methodology of these clinical studies is known to be weak. We attempted to quantify these methodological weaknesses. Our results suggest that the level of evidence does not necessarily increase with the level of risk and that the clinical evidence used to demonstrate safety and efficacy for high-risk medical devices is actually based on clinical studies with poor-quality data. Focusing on particular examples of innovative medical devices, we showed that less than 18% of the clinical studies relating to high-risk medical devices provided high-quality data. By contrast, for class I medical devices, most of the clinical studies produced high-quality data. These results are consistent with the results of another French team who studied the level of evidence of studies on implantable devices [11]. Their study was based on the expert opinion of the CNEDiMTS published in 2008 and publicly available from the web site of the French National Authority for Health. Less than half of the clinical studies with the highest level of evidence assessed by the CNEDiMTS during 2008 were prospective randomized controlled studies or meta-analyses of prospective randomized controlled studies.

Our analysis also highlighted methodological issues relating to studies of medical devices. Indeed, the randomized controlled studies commonly used for drug studies are considered the 'standard' for establishing the efficacy and safety of medical products [12]. However, this methodology is difficult to apply to many medical devices, as demonstrated by our results. Less than one-quarter of the 215 studies were randomized controlled studies. This problem has already been highlighted in previous studies [13–15] and results from a reluctance to randomize patients when the control device is considered to be technologically inferior. Randomization is particularly difficult when comparing surgical medical devices with other therapeutic alternatives [16]. Furthermore, most of the clinical studies concerning surgical medical devices are retrospective studies or case reports and less than 10% are studies with high-quality data [17]. Blinding is difficult to achieve particularly for highly invasive medical devices and for comparisons between medical devices and drug treatments or surgical interventions. Thus, for technical and ethical reasons, the blinding issue is impossible to overcome [18].

The use of a placebo or a sham intervention is difficult in many instances for medical devices. In our analysis, only one study had a placebo control group.

More than half of the 215 studies included fewer than 30 patients. The use of a small sample size may decrease the power of the study and make it pore difficult to detect differences between treatments in terms of effectiveness or unusual side effects [14]. Moreover, sample size calculations were not sufficiently reported in the published articles. This problem is not specific to trials for medical devices, but sample size is a recurring issue for these medical products [15]. A survey performed between January 2005 and December 2006 screened 215 publications concerning pharmacologic and non-pharmacologic randomized controlled trials (RCTs) and showed that sample size calculations were adequately described in less than one-third of these studies [19]. Our results are consistent with those of this survey, which reported that less than 40% of the articles with high-quality data reported sample size calculation.

Sample size is calculated as a function of the principal clinical outcome and there should be only one primary outcome in a clinical trial [14]. In many instances, particularly due to small sample sizes, outcomes are combined to yield a 'composite end point'. This can affect the results of the clinical trial by masking outcomes operating in opposite directions, for example, or in cases of rare but catastrophic events.

For implantable medical devices, CE marking is usually obtained in the absence of long-term clinical data. A long follow-up period is therefore required to assess the efficacy and safety of these devices. The mean follow-up period for the studies included in our analysis was 18.9 months, which seems very short given the long duration of use of such devices. Interventional studies with long-term follow-up are clearly not feasible. Nevertheless, it would be interesting to conduct observational studies followed by comparative studies to provide complementary data [15].

Limitations

In this study, the number of innovative medical devices was limited to 32. It was therefore not possible to extrapolate the results concerning the level of evidence to all innovative medical devices coming onto the market. Nevertheless, we analyzed a significant number of publications (217 studies). Our principal objective was to look at shared experience in the field and to show how difficult it is to evaluate innovative medical devices in a practical and timely way for decision support. Another possible bias results from the overrepresentation of cardiovascular devices due to the specialization of our hospital. The results for cardiovascular devices may be different from those for devices in other specialties.

We used the EuroScan International Network definition of an innovative device, but this may have resulted in our incorrectly considering several medical devices to be innovative. Indeed, the definition of an innovative medical device is not consensual and is subject to individual interpretation.

We also encountered certain other difficulties such as assessment of the learning curve for the devices. The learning curve is defined as the time or number of procedures required for an average surgeon to be able to perform a procedure independently with an acceptable outcome [20]. The presence or absence of a learning curve seems to be important and should be noted in publications concerning new medical devices, particularly for implantable devices [14]. Moreover, certain related factors, such as the volume–outcome relationship and threshold volumes, should be reported to determine whether the degree of experience or mastery of the technique affects outcomes [21]. Only a few articles tackled these points, making their assessment difficult.

The 2007/47/EC directive allows manufacturers to use clinical data for other similar medical devices to support applications for CE marking. However, this directive did not really define the criteria to be used to determine equivalence. This ambiguity of European regulations made the interpretation of equivalence very difficult for several of the medical devices in our study (coated balloons, endoprosthesis for abdominal aortic aneurysm, etc.). More generally, it enables manufacturers to circumvent the directive and avoid having to carry out clinical investigations for high-risk medical devices [4]. CE marking is thus often delivered after a simple demonstration of equivalence with another device subject to clinical evaluation. This hypothesis is supported by a recent French Senate report on the safety of medical devices [22]. Indeed, this report states that 90% of the medical devices on the French market obtained their CE marking after a demonstration of equivalence. This issue is also a key matter of debate in the USA [23,24]. Indeed, safety and efficacy concerns have been raised for implantable devices approved through the FDA (U.S. Food and Drug Administration) 510k procedure. This premarket notification is designed to all the manufacturers to make a pre-market submission to the FDA, demonstrating that the medical device to be marketed is at least as safe and effective as a legally marketed device. For this, the device must be considered 'substantially equivalent'. In the face of increasing numbers of challenges to the 510k process, the US Institute of Medicine has suggested the replacement of this process with an evaluation of safety and effectiveness [23,25].

Conclusion

The level of evidence, as established by Sackett *et al.*, ranks the RCT as the 'gold standard' of clinical trials. This methodology is appropriate for drugs, but may not necessarily be appropriate for medical devices [12]. An adaptation of the classification of levels of evidence to specific features relating to medical devices would be required for the correct evaluation of data quality. For example, the learning curve or the volume–outcome relationship would need to be reported in the published articles [14]. Furthermore, health professionals working in hospitals should contribute to the development of post-marketing studies. This will require them to be trained to deal with specific aspects of medical devices [18]. Finally, no further progress is likely to be made until medical devices regulation in Europe is modified. The European Commission is proposing a new regulatory system for medical devices based on a recasting of the old directives [26]. As already pointed out by many authors, the new regulations will require high-quality studies demonstrating clinical efficacy/effectiveness before approval for market release is given [2,4,27,28]. Nevertheless, it will take some time for the beneficial effects of the new regulations to materialize.

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