

# **Assessment and diffusion of biotechnology drugs**

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Assessment and diffusion of biotechnology drugs  
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# **Assessment and diffusion of biotechnology drugs**

Beoordeling en diffusie van biotechnologische geneesmiddelen

(met een samenvatting in het Nederlands)

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## CONTENTS

|    |   |     |
|----|---|-----|
| 1  | Introduction  | 7   |
| 2  | Assessment of biotechnology drugs: what are the issues?   | 21  |
| 3  | Differences in attitudes, knowledge and use of economic evaluations in decision-making in the Netherlands: the Dutch results from the EUROMET project       | 45  |
| 4  | Cost-efficacy in interventional cardiology: results from the EPISTENT study   | 63  |
| 5  | Costs and effects of combining stenting and abciximab (ReoPro®) in daily practice   | 81  |
| 6  | Variability in abciximab (ReoPro®) prescribing: evidence based or budget driven?  | 91  |
| 7  | The diffusion of recombinant Factor VIII: a study of patients' preference   | 103 |
| 8  | The diffusion of recombinant Factor VIII: a study of physicians' preference   | 119 |
| 9  | From human menopausal gonadotropins (hMG) through purified urinary follicle stimulating hormone (FSH) preparations to recombinant FSH: a substitution study | 131 |
| 10 | Summary and general discussion  | 151 |
|    | Samenvatting  | 167 |
|    | Dankwoord   | 173 |
|    | Curriculum vitae  | 175 |

# 1

## Introduction



## **BIOTECHNOLOGY**

New medicines are an important part of innovation in medical care. Advances in genomics, biotechnology and other innovative areas in the biopharmaceutical sciences fuel the surge in new active compounds for unmet medical needs [1,2]. It has been predicted that the combination of genomics, bioinformatics and structural genomics will generate unprecedented results in the new century, which will revolutionise medicine [3-6].

In 1978, researchers first reported that they had been able to express the human insulin gene in *E. Coli* [7]. In the late 1970s and early 1980s high expectations have been placed on the young biotechnology industry. A 1984 cover of *The Economist* read: 'The genetics gold rush' [8]. Some, but not all of the dreams of that time have come true. The first recombinant molecules to be developed, human insulin and growth hormone, have been successfully introduced to the market. Interferon, however, did not come through as the magic cure for cancer that it was supposed to be, and several biotech compounds, such as for example nebacumab, have failed as a treatment for sepsis [9,10]. During the late 1980s and the early 1990s the initial enthusiasm for the biotechnology industry faded [11]. On a 1994 cover of *BusinessWeek* the question was even raised: 'Biotech, why it hasn't paid off' [12].

Nevertheless, in 2000, more than 50 biopharmaceuticals were commercially available on the Dutch market (see Table 1). By now biopharmaceuticals are fully integrated in everyday's medical practice. In the top 10 drugs most prescribed by specialists in 1999, 3 biotech were present (Table 2) [13]. During the past few years the biotech hype has even revived again, not in the least due to the Human Genome Project which was completed in 2000 [14,15]. The number of innovative biopharmaceuticals on the market will probably continue to rise, and, in addition, high hopes are set on gene therapy, medication adapted to one's gene profile (pharmacogenetics), and improved diagnostic possibilities [16-19]. The genetics gold rush is re-opened again, and while the internet and information technology funds experience bad times, new biotech funds continue to appear on the stock markets [20,21].

## **DIFFUSION AND TECHNOLOGY ASSESSMENT**

On the one hand, these medical developments are greeted by society with great enthusiasm, as they give hope for future cures for diseases like cancer and HIV. Advances in medical research and technology are often the last straw for people suffering from serious disease. However, there is also fear for the continuous advance of science and technology. In the public opinion genetic engineering is sometimes associated with the danger of its usage to eliminate displeasing races and create 'super humans' [22,23].



**Table 1** Biotechnology drugs approved in the Netherlands until May 2001

| <b>Brandname</b> | <b>Chemical name</b>  | <b>Brandname</b> | <b>Chemical name</b>     |
|------------------|-----------------------|------------------|--------------------------|
| Actilyse         | Alteplase             | Pulmozyme        | Dornase alfa             |
| Avonex           | Interferon beta-1a    | Puregon          | Follitropin beta         |
| BeneFix          | Factor IX             | Rapilysin        | Reteplase                |
| Beromun          | Tasonermin            | Rebif            | Interferon beta-1a       |
| Betaferon        | Interferon beta-1b    | Recombinate      | Factor VIII              |
| Bioclata         | Factor VIII           | ReFacto          | Moroctocog alfa          |
| Cea-Scan         | Te-99m-arcitumomab    | Refludan         | Lepirudine               |
| Cerezyme         | Imiglucerase          | Regranex         | Becaplermin              |
| Enbrel           | Etanercept            | Remicade         | Infliximab               |
| Eprex (alfa)     | Epoetine alfa         | Reopro           | Abciximab                |
| Forcaltonin      | Calcitonin, salmon    | Roferon-A        | Interferon alfa-2a       |
| Genotropin       | Somatropin            | Simulect         | Basiliximab              |
| Glucagen         | Glucagon              | Synagis          | Palivizumab              |
| Gonal-F          | Follitropin alfa      | Thyrogen         | Thyrotropin alfa         |
| Granocyte        | Lenograstirn          | Viraferon        | Interferon alfa-2b       |
| Helixate         | Factor VIII           | ViraferonPeg     | Peginterferon alfa-2b    |
| Herceptin        | Trastuzumab           | Zenapax          | Daclizumab               |
| Humaspect        | Votumumab             | Zomacton         | Somatropin               |
| Humatrope        | Somatropin            | <b>Insulins:</b> |                          |
| Immukine         | Interferon gamma-1b   | Actrapid         | Insulin, normal          |
| Infergen         | Interferon alfacon-2  | Humaject         | Insulin, normal          |
| Intron A         | Interferon alfa-2b    | Humalog          | Insulin lispro           |
| Kogenate         | Factor VIII           | Humuline         | Insulin, normal          |
| Leucomax         | Molgramostim          | Insulatard       | Insulin isophane         |
| LeukoScan        | Sulesmab              | Insuman          | Insulin, normal          |
| Mab Thera        | Rituximab             | Isuhuman         | Insulin, normal          |
| Metalyse         | Tenecteplase          | Lantus           | Insulin glargine         |
| NeoRecormon      | Epoetine beta         | Mixtard          | Insulin, normal          |
| Neupogen         | Filgrastim            | Monotard         | Zinc insulin, amorph     |
| Norditropin      | Somatropin            | Novomix          | Insulin aspart           |
| Novoseven        | Factor VIIa           | Novorapid        | Insulin aspart           |
| Orthoclone OKT 3 | Muromonab-CD3         | Optisulin        | Insulin glargine         |
| PEGIntron        | Peginterferon alfa-2b | Ultratard        | Zinc insulin, cristaline |
| Proleukin        | Interleukin-2         |                  |                          |

Source: Nefarma

In Europe there is considerable resistance against genetically modified food [24-26]. Although high tech developments strike the imagination, there is also a movement visible towards more attention for essential and intrinsic values, and for 'caring for' and 'standing by' patients. Natural and holistic remedies enjoy large popularity [27,28].

**Table 2** Top 10 prescriptions by specialists in Dutch community pharmacies in 1999

|    |                    | <b>Costs (million Euros)</b> |
|----|--------------------|------------------------------|
| 1  | Omeprasol          | 30.9                         |
| 2  | Simvastatin        | 20.0                         |
| 3  | Atorvastatin       | 16.3                         |
| 4  | Somatropin         | 12.3                         |
| 5  | Human insulin      | 11.8                         |
| 6  | Mesalasin          | 10.9                         |
| 7  | Goserelin          | 9.5                          |
| 8  | Budesonide         | 9.1                          |
| 9  | Ciclosporin        | 8.6                          |
| 10 | Interferon beta-1a | 8.6                          |

Source: *Stichting Farmaceutische Kengetallen*

Not all that is possible is desirable. We do not want science and technology to evolve autonomously, without society having say in it [29,30]. The average citizen or politician, however, is not well enough informed to sensibly weigh the possible benefits and risks of scientific advancements. That's where Technology Assessment (TA) came in. In 1972, the United States installed the Office of Technology Assessment (OTA), in order to provide the senators with systematic and structured overviews of advantages and disadvantages as an input to decision making [31]. The 'Health Programme' was one of the first and most extensive programs of the OTA. The start of this programme in 1975 has been marked as the birth of Medical Technology Assessment (MTA) [31-33].

The emergence of MTA coincides with a development towards the rationalisation of medical practice. In the early postwar period medical practice was seen foremost as an art, and not so much as a science. During the past decades, however, the scientific character of medical practice was more and more emphasised. For the first time, this made it possible to judge and scrutinise medical practice (increased accountability) [34]. Movements such as MTA, creating protocols and guidelines, and evidence based medicine stem from the desire to render medical practice more scientific.

However, as Rogers [35] describes in his book on the diffusion of innovations, the perceived medical advantage is not the only variable determining the rate of adoption of a new drug. Other variables such as the nature of the social system and the extent of promotion efforts have an influence as well. The assessment of biotechnology drugs takes place at different levels. Politicians, regulators and health care insurers have to decide about the licensing and reimbursement of pharmaceuticals. Specialist organisations and formulary committees develop good

practice guidelines. On the lowest level, physicians, often together with their patients, choose individual treatment strategies. Since these decision-makers operate in different social systems and act from different perspectives, their interests may also differ. Together, the different stakeholders shape the diffusion pattern of a new biotechnology drug.

### **COST CONTAINMENT**

While the medical possibilities continue to advance, the health care costs have increased during the past decades and cost containment has been an important goal for policy makers [36-38]. Especially medicines have received a lot of attention, as they represent a relatively easy target to take on [39-41].

Measures taken to control extramural expenditures include for example the reimbursement cluster system (GVS, 1991) and the reference pricing system (Wet Geneesmiddelenprijzen, 1996) [41,42]. Within hospitals drug expenditures are covered by the general budgeting systems. Notwithstanding these measures, the costs have continued to grow, and recently 3 separate groups of investigators in their advice to the Minister each concluded that these measures are not sufficient anymore [43-45]. This led to a paradigm shift from a supply driven to a demand driven orientation. The current trend is towards regulated competition among insurers (and among providers), in which health care insurers should be the critical buyers of high quality and efficient care for their insured [46]. Doubts remain whether the insurers have the knowledge and the expertise to fulfil this task. In addition, measures have to be taken in order to maintain solidarity and to prevent risk selection by the insurers. Biotechnology drugs are generally expensive drugs, which are prescribed for serious diseases and are often used inside the hospital. A high price per treatment or per patient attracts the attention and also it worries payers, since it means that a small increase in volume can cause a large increase in costs [47-49]. The Health Insurance Fund Council (CVZ) advocates including a pharmacoeconomic evaluation in the assessment of new and expensive drugs [50]. Politicians, however, operating from a budget oriented environment, find themselves in a difficult position when they have to explain that not everything that can be done should be done, while at the same time they are confronted with patients whose individual sorrows are hardly proportionate to strict budget keeping. In the health care sector, a politician can hardly afford himself to be a 'bookkeeper'. While the Minister of Health is trying to contain the use of expensive (biotech) pharmaceuticals, the Minister of Economics is investing €50 million to stimulate the establishment of young biotech start-ups in the Netherlands [51].

## **AIMS AND OUTLINE OF THE THESIS**

The general aim of this thesis is to explore the broad field of the assessment and the diffusion of biotechnology drugs (Table 3). The research was conducted by means of case studies of particular biotechnology drugs, except for one study that concerned the general attitude of decision-makers towards economic evaluations (Chapter 3). Case studies provide an appropriate mean to generate insights, and to explore a broad and relatively new field.

The next paragraphs discuss the specific aims of the different chapters.

### ***Medical Technology Assessment***

To investigate the factors that are important in the process of the assessment of biotechnology drugs, in Chapter 2 we collected data on three biotechnology drugs that were chosen to cover a broad range of potentially relevant issues: nebacumab, filgrastim and recombinant human growth hormone (rhGH). Nebacumab (Centoxin®), a drug for the treatment of Gram-negative sepsis, could be considered a failure, since it had only been on the European market for 2 years. In the United States it had never received marketing approval. In contrast, filgrastim (Neupogen®), a granulocyte colony-stimulating factor, was a very successful product that was generating a lot of profit [52]. Although filgrastim is fairly expensive, its value did not seem to be questioned. Recombinant hGH has been a successful drug as well, but it encountered much more concern about unwarranted use and a lack of long-term utility. Moreover, this biotechnology drug had substituted the previously used pituitary derived compound.

The data for analysis were collected from scientific papers and government reports. They were analysed in a standardised way covering: 1) safety, 2) efficacy/effectiveness, 3) economic evaluation, and 4) ethical, legal and social factors [32].

### ***Economic evaluation and abciximab***

The objective of Chapter 3 was to investigate differences in attitudes, knowledge and actual use of economic evaluations in four different groups of decision-makers: 1) politicians, 2) regulators, 3) hospital pharmacists and 4) physicians. The methods used were individual interviews with decision-makers and a postal questionnaire. This study was conducted within the framework of the European Network on Methodology and Application of Economic Evaluation Techniques (EUROMET) project. The Dutch results were compared with the overall results from all countries participating in the EUROMET project.

**Table 3** Content of the thesis

|                       |  | <b>Subject matter</b>   |                            |  |   |  |
|-----------------------|--|---|----------------------------|--|---|--|
| <b>Focus of study</b> | <b>Assessment</b>  | <b>General</b>  | General                    | Expensive new biotech drug<br><br>- <i>abciximab</i>   | Biotech substitute for existing compound<br>- <i>factor VIII</i><br>- <i>follitropins</i> |  |
|                       |  |   | <b>Economic evaluation</b> | <b>Chapter 2</b><br>Structured description of 3 biotech cases (nebacumab, filgrastim and recombinant human growth hormone) |   |  |
|                       |  |   |                            | <b>Chapter 3</b><br>Decision makers' opinions on health economics  | <b>Chapter 4</b><br>CEA of abciximab alongside a clinical trial                           | <b>Chapter 5</b><br>CEA of stenting combined with abciximab in real practice |
|                       | <b>Chapter 6</b><br>Abciximab usage in different Dutch hospitals | <b>Chapters 7 &amp; 8</b><br>Plasma Factor VIII → recombinant Factor VIII |                            |  |   |  |
|                       |  |   |                            | <b>Chapter 9</b><br>Urinary gonadotropins → recombinant follitropins   |   |  |
|                       | <b>Diffusion</b>   |   |                            |  |   |  |

CEA=cost-effectiveness analysis

Abciximab (ReoPro®), a glycoprotein IIb/IIIa receptor blocker, has been shown to be effective in reducing the rate of myocardial infarction and the necessity for urgent revascularisation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) [53-56]. Intracoronary stents have been shown to reduce the need for repeat revascularisations by 20-50% [57-63]. In the 'Evaluation of Platelet IIb/IIIa Inhibitor For Stenting Trial (EPISTENT)' study the combined use of stents and abciximab was studied and turned out to be superior to either stenting or abciximab administration alone [64,65]. In Chapter 4 the question was addressed on the balance between the costs and effects of combined use of abciximab and stenting, using the efficacy data from the EPISTENT study in combination with Dutch estimates of unit costs. Assessed were both the cost-efficacy of adding a stent to a procedure where the use of abciximab is planned, and the cost-efficacy of adding abciximab to a procedure where the use of a stent is planned. Special attention was given to the uncertainties surrounding the estimates, especially when breaking down the results between diabetics and non-diabetics.

The clinical and economic findings in clinical trials are not necessarily generalisable to a general population setting. Therefore, in Chapter 5, a study was conducted in daily clinical practice comparing stented and non-stented patients undergoing coronary angioplasty with abciximab administration. The results were compared with the findings of the EPISTENT trial.

In the Dutch health care system all hospitals are budgeted. In the media cardiologists have expressed their concern that their budgets do not allow them to give abciximab to all eligible patients. Public exposure of this issue has been high. In Chapter 6, the patterns of prescribing of abciximab were studied and factors that determine the level of usage were identified. All thirteen PTCA centers in the Netherlands participated in the study.

### ***Diffusion of biotech substitutes***

Starting in 1982 with the introduction of recombinant human insulin, several biotechnology drugs have been launched as an alternative to similar, already existing compounds purified from organic materials such as pituitaries, urine and blood (Table 4). These biotechnology substitutions constitute well-defined cases to investigate the diffusion of biotechnology drugs.

The first case presented in this thesis is the case of recombinant Factor VIII (rFVIII), which was introduced in the Netherlands in 1995 for the treatment of hemophilia A. Until then, hemophilia patients had been treated with plasma derived Factor VIII (pdFVIII), the main provider of which was the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service. Seventeen percent of all Dutch patients with severe hemophilia who were treated with clotting factor products before 1985 became infected with the human immunodeficiency virus (HIV) [66,67]. In addition,

the large majority (about 80%) of patients have been infected with hepatitis C virus [68,69]. Because of this history of infectivity with pdFVIII one may have expected that rFVIII would receive a warm welcome and would be quickly adopted by the market. This, however, has not been the case.

**Table 4** Overview of biotech substitutions

| <b>Recombinant compound</b>      | <b>year of introduction*</b> | <b>substitute for</b>            |
|----------------------------------|------------------------------|----------------------------------|
| human insulin                    | 1982                         | porcine and bovine insulin       |
| human growth hormone             | 1985                         | pituitary derived growth hormone |
| alteplase (tPA) and<br>reteplase | 1988 and 1999                | streptokinase and urokinase      |
| Factor VIII                      | 1995                         | plasma derived Factor VIII       |
| follitropins                     | 1996                         | urinary gonadotropins            |
| Factor IX                        | 1997                         | plasma derived Factor IX         |

\* Year of introduction to the Dutch market, tPA= tissue plasminogen activator

We sent a postal questionnaire to both patients (Chapter 7) and hemophilia treating physicians (Chapter 8) to investigate their opinions on rFVIII as compared to pdFVIII, and to determine which factors predict whether someone uses pdFVIII or rFVIII.

The second substitution case concerned the gonadotropins. Among other indications, gonadotropins are used for ovarian hyperstimulation in in-vitro fertilisation. Human Menopausal Gonadotropins (hMG), containing both Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH) derived from the urine of postmenopausal women, have been commercially available since the 1960s. During the 1980s and the early 1990s urinary derived products with an increased purity were developed, containing only FSH and hardly any LH. Subsequently, in 1996 the first follitropin (=recombinant FSH) was introduced. The aim of Chapter 9 was to describe the diffusion patterns of these different types of gonadotropins in the Netherlands and to obtain insight in the processes underlying these patterns. We used clinical sales data, and analysed data on pivotal articles published, product introductions and withdrawals, reimbursement decisions, and the like.

The results of this thesis are summarised and discussed in Chapter 10.

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## Chapter 1

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# 2

## **Assessment of biotechnology drugs: what are the issues?**

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## ABSTRACT

*Background* - Biotechnology is increasingly regarded upon as an important reservoir for the development of new and innovative but generally expensive, pharmaceuticals. At the same time, concerns about cost containment have triggered a keen interest in evaluating and comparing the values of diverse health care interventions.

*Aim and methods* - In this paper we studied the process of assessment and diffusion of biotechnology drugs by studying three cases, i.e. nebacumab, colony stimulating factors and recombinant human growth hormone. These cases are evaluated in a standardised format, concerning safety, efficacy, cost-effectiveness and ethical, legal and social issues.

*Results* - Many factors that determine the fate of a biotechnology drug seemed to be similar to those of 'classical' drugs. The definition and measurement of clinically relevant outcomes has been identified as a key factor in the assessment process. Another important issue is the relatively small population for the primary indications of biotechnology drugs and the subsequent process of broadening of indications.

*Conclusion* - Paradoxically, the current trend towards evidence based medicine means that we will increasingly have to make decisions based on 'incomplete knowledge'.

## **INTRODUCTION**

In the pharmaceutical sector a new category of drugs has emerged: biotechnology drugs [1]. Starting with the introduction of recombinant insulin and recombinant growth hormone in the early 1980s, many pharmaceutical proteins have entered the market which are produced by cell cultures of genetically modified cells, mostly bacteria [1, 2]. Many of them are indicated for the treatment or prevention of serious life threatening diseases [1].

The rapid clinical success of the first recombinant proteins drove large investments and placed high expectations on this young industry [3]. Analysts predict that in the long term, about 20-25% of the world drug market will be supplied with products based on genetic engineering methods [4]. Pharmaceutical products derived from European biotechnology are expected to grow by 15% per year [5]. Clearly, the early promise of pharmaceutical biotechnology has been, and still is, enormous.

On the other hand, it has been noted that applications for new biotechnology drugs to the FDA were highly successful in the early period between 1980 and 1984, but that current success rates are lower and do not exceed the success rates for 'classical' drugs [3]. Notwithstanding the early promises, clearly not all biopharmaceuticals have been proven to be efficacious and safe [3]. From a list of 22 potentially important protein drugs, only about one third are in practical use today [6]. It has been acknowledged that, in spite of great progress, pharmaceutical companies still cannot create gold. However, it has been stated that the pharmaceutical companies scarcely need to [7]: 'Gold is worth a mere US\$10 a gram. Human growth hormone, as synthesised by Genentech, sells for the equivalent of more than US\$20,000 a gram.' It is true that recombinant proteins are generally expensive and weigh heavily on the annual drug budget [6].

Most developed countries currently spend about 10% of their gross domestic product on health care [8, 9]. Expenditures are on the rise due to the general ageing of the population and the introduction of new medical technologies. Pharmaceutical expenses increase much faster than health care expenditures in general. In the Netherlands for example, pharmaceutical expenses showed an average annual growth of more than 7% during the period 1982-1995, while in the same period the growth of health care expenses amounted to 3.5% [10]. As a consequence awareness is growing amongst the parties involved of the need for a more efficient use of the available resources [8].

The availability of expensive biotechnology drugs, also raises ethical problems in some instances, especially with regard to the limits of ethically justified use (e.g. growth hormone, colony stimulating factors), or abuse (epoetin, growth hormone).

The assessment of biotechnology drugs takes place at different levels. Besides the assessment for registration and reimbursement on a macro level, products are also assessed on a meso and micro level by specialist organisations and formulary

commissions in hospitals and by individual practitioners [11]. The fate of a biotechnology drug, its adoption and diffusion, is determined by these assessments and decisions. The process of assessment, however, is not merely a rational process based on facts only; politics is inevitable [12, 13]. The players in the health care field, industry, patient organisations, physicians, insurers and government authorities, each have their own values, which influence their selection and interpretation of evidence considered relevant. The degree of impact that they can exert on the decision-making process may differ [12].

In order to study the factors that are important in the process of the assessment of biotechnology drugs, we collected data on three pharmaceutical recombinant proteins: nebacumab, filgrastim and recombinant human growth hormone. These data were assessed in a standardised way to determine which are relevant issues in the assessment process and which parameters are important for a biotechnology drug to be successful.

### **METHODS AND SELECTION OF CASES**

For this study we chose three cases that, at first sight, had very different characteristics and could present a good mix of possible issues that play a role in the assessment and diffusion process of biotechnology drugs, namely nebacumab (Centoxin®), colony stimulating factors (focusing on filgrastim; Neupogen®) and recombinant human growth hormone (several products/brands).

Nebacumab can be considered a failure, since it has only been on the European market for two years. In the United States it has never received marketing approval.

In contrast, filgrastim is a very successful product that is generating a lot of profit [14]. Although filgrastim is fairly expensive, its value does not seem to be questioned. Filgrastim is a member of the family of colony stimulating factors, which form a subgroup of the hematopoietic growth factors. Although several pharmaceutical differences between the various the colony stimulating factors exist, in this study filgrastim represents the case of the colony stimulating factors in general. In review articles and clinical guidelines the colony stimulating factors usually are treated as one group of equivalent drugs. Although this approach may not be entirely correct, it is representative of the general way of dealing with these medicines, which is the subject of this study.

Recombinant human growth hormone (rhGH) has been also a successful drug, but it encounters much more concern about unwarranted uses and a lack of long-term utility. This recombinant protein has substituted the previously used pituitary derived compound. Several products and brands are on the market, with slightly different pharmaceutical characteristics. Even more than the colony stimulating factors, they are generally described as one group. We adopted this approach and described rhGH in general, without focusing on a single representative brand.

To structure the different factors that may be important in the process, we looked at: 1) safety, 2) efficacy/effectiveness, 3) cost-benefit/cost-effectiveness/cost-utility and 4) ethical, legal and social factors [15]. The data for analysis were collected from scientific papers and government reports. The three cases were analysed by these categories and subsequently a comparison was made to draw conclusions as to which extent the similarities and differences between these cases could give us more insight in the process of assessment and diffusion of biotechnology products.

## **DESCRIPTION OF CASES**

### ***Nebacumab***

Nebacumab (HA-1A, Centoxin®) is a human monoclonal antibody that in vitro binds specifically to endotoxin, a compound of the cell envelope of Gram-negative bacteria. The antibody was produced by Centocor and was thought to be effective in the treatment of Gram-negative bacteremia (the presence of Gram-negative bacteria in the blood). To confirm a Gram-negative bacteremia, a blood culture has to be performed. However, because Gram-negative bacteremia may have a rapidly fatal course, treatment has to be started before the results of the blood culture are available (this takes 48 hours). In four large trials that used entry criteria that met the definition of severe sepsis, only 20-40% of the patients turned out to have Gram-negative bacteremia [16].

Application for marketing authorisation of nebacumab in Europe was requested by Centocor in February 1990, through a European procedure for approval of biotechnology products by the Committee for Proprietary Medicinal Products (CPMP). The CPMP decided in March 1991 that there was sufficient evidence for efficacy of the drug and recommended marketing authorisation to its member states [17]. On April 4, 1991 nebacumab was registered in the Netherlands, being the first country in the world. However, in the United States the drug was denied approval by the FDA, based on the same clinical trial conducted by Ziegler et al. [18]. To meet the FDA's requirements, Centocor started a second trial, the CHES trial [19]. This trial was stopped at the first interim analysis, because of excess mortality in the treatment group. Shortly after that, the distribution of nebacumab was stopped (Table 1).

### ***Safety***

In the first trial conducted by Ziegler et al., no important side-effects were found in the complete study population [18]. However, in a subgroup of patients who turned out not to have had Gram-negative bacteremia, mortality was higher in the nebacumab arm (45%) than in the placebo arm (40%;  $p=0.36$ ) [20]. Initially, not much attention was paid to this observation.

**Table 1** History of nebacumab

|                   |  |
|-------------------|--|
| February, 1990    | Centocor applied with CPMP for a marketing authorisation |
| February 14, 1991 | <i>N Engl J Med</i> : publication of Ziegler's data      |
| March, 1991       | CPMP approved application                                |
| April, 1991       | Nebacumab's first registration (in the Netherlands)      |
| September 4, 1991 | FDA Advisory Committee Hearing                           |
| April 15, 1992    | FDA denies approval                                      |
| April 23, 1992    | <i>N Engl J Med</i> : Warren, Wenzel and Ziegler         |
| June, 1992        | Start of CHES trial                                      |
| January, 1993     | CHES trial suspended                                     |
| January 20, 1993  | Distribution of nebacumab stopped                        |

*CPMP=Committee for Proprietary Medicinal Products, FDA=Food and Drugs Administration*

The CHES trial, however, was stopped after the first interim analysis, because in patients who did not have Gram-negative bacteremia, the mortality rate was significantly higher in the nebacumab treated group than in the placebo group ( $p=0.09$ ). In patients who did have Gram-negative bacteremia (28%), the mortality rate in both groups was practically the same [19]. This result led to the total removal of nebacumab from the market.

### *Efficacy/effectiveness*

The robustness of the preclinical data and the rationale for starting clinical studies have been disputed. There has been discussion about the binding characteristics of nebacumab and about the fact that nebacumab had not consistently protected animals from endotoxic challenge in experimental models [21-23]. The high species specificity of nebacumab hindered the design of appropriate animal models [22-24]. Some people felt that the company developed the product too fast because of the competition [25].

Efficacy has been the most important issue in the nebacumab case. The efficacy as demonstrated by Ziegler's trial was disputed. In the total population no significant difference could be demonstrated; a significant decrease in mortality through the use of nebacumab was found only in the subgroup of patients with confirmed Gram-negative bacteremia [18]. The trial produced a lot of criticism, including that the level of significance was marginal [26]; that patient characteristics were different in the placebo and the treatment group [21, 27]; and that the primary endpoint of the study had been changed, after the results of the first interim analysis became known to the Centocor staff [26]. In particular this last point was the reason for the FDA to deny approval and demand a second trial [26].



Before this trial was stopped prematurely, 621 patients with confirmed Gram-negative bacteremia were included. Efficacy of nebacumab was not demonstrated; mortality rates in treatment and placebo group were 33% and 32%, respectively ( $p=0.86$ ) [19].

The identification of targeted patients presented another problem in the nebacumab case. It was not possible to identify patients with Gram-negative bacteremia before the onset of treatment. Work has been done to develop a test to determine the level of endotoxins in the blood [28-32]. However, up until now such a method is not available.

#### *Cost-benefit/cost-effectiveness/cost-utility*

Costing over US\$ 3000 dollars a dose, nebacumab was one of the most expensive drugs ever, and raised many concerns in this respect [33]. From 1991 to 1993 three cost-effectiveness studies on nebacumab were conducted [34-36]. Schulman et al. [34] concluded that the use of nebacumab could add US\$2.3 billion to the annual U.S. health care budget, if the treatment guidelines were strictly adhered to. He also included a 'test scenario' in his study, in which the availability of a quick and reliable testing method is presumed, so that only patients with known Gram-negative bacteremia would receive nebacumab. Obviously, the cost-effectiveness of nebacumab was generally lower in this scenario, depending on the sensitivity and specificity of the hypothetical diagnostic test.

Although, Van Hout [36] noted that the cost per life year gained compared favourably with other health care programs, nebacumab never lost the image of being expensive. This idea has probably attributed significantly to the call for better criteria to identify the patients to whom the product might be beneficial. Both in the United States (before the FDA denied approval) and in Europe hospitals established guidelines for the prescription of nebacumab [29, 37, 38]. It seems that economic considerations were the driving forces to draw up guidelines, rather than the concern that some patients may be unnecessarily exposed to the adverse effects of a drug that was not effective for them.

#### *Ethical, legal and social issues*

It is remarkable that the FDA and the CPMP reached two different decisions based on the same data. There are several factors that might have influenced the CPMP's decision to approve nebacumab. Firstly, nebacumab represented a new and attractive therapeutic approach awaited for more than 10 years. Secondly, it proposed a treatment for a highly fatal disease, for which only limited therapeutic possibilities exist. Moreover the application was filed by a company whose whole future depended on this one innovative product [17, 37].

As Luce described in his article, the decisions to be made about the use of nebacumab raised an ethical dilemma, especially in American hospitals that cared for a large number of unsponsored patients. The physicians wanted their patients to receive the best possible treatment and they were concerned that not using nebacumab while physicians elsewhere were using the drug would constitute malpractice. On the other hand they were aware that adding nebacumab might require the removal of other drugs from the formulary [37]. This ethical issue is, of course, strongly related to the cost factor.

### ***Colony stimulating factors: filgrastim***

Filgrastim is a member of the family of hematopoietic growth factors (HGFs), which consists of granulocyte colony-stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO) and others. Filgrastim is a G-CSF, produced by Amgen through an *E. coli* bacteria into which has been inserted the human G-CSF gene. It regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation and cell functional activation. In 1991 filgrastim received marketing authorisation to decrease the incidence of infection as manifested by febrile neutropenia for patients undergoing chemotherapy (Table 2). Subsequently the drug was also registered for the treatment of chronic neutropenia, to reduce the duration of neutropenia after bone marrow transplantation and to support peripheral blood progenitor transplantation (PBPC transplantation). In 1994 (update in 1996) the American Society of Clinical Oncology (ASCO) conducted a literature review and formulated recommendations for the use of hematopoietic colony-stimulating factors [39, 40].

### ***Safety***

So far very little evidence of serious side-effects has been shown. The ASCO Guidelines report that the predominant side effect associated with administration of G-CSF has been medullary bone pain. This effect is reported in 15-40% of patients receiving an average dose [39].

### ***Efficacy/effectiveness***

Neutropenia and infection are major dose limiting side effects of chemotherapy. Patients who present with fever usually are hospitalised and given intravenous broad spectrum antibiotics. In current practice, infectious mortality resulting from febrile neutropenia is about 10% [41-43]. Moreover episodes of febrile neutropenia may result in subsequent chemotherapy delays or dose reductions.

| <b>Table 2</b> | History of filgrastim   |
|----------------|---|
| February, 1991 | Registration in Europe and in the US to decrease the incidence of febrile neutropenia in patients undergoing chemotherapy   |
| 1992-1997      | <i>Registration for additional indications:</i><br>to reduce the duration of neutropenia after BMT<br>to treat patients with severe chronic neutropenia<br>to support PBPC transplantations<br>to treat neutropenia in people with advanced HIV infection |
| Present time   | Research for new indications in disease- and treatment related cytopenia and in infectious diseases   |

*PBPC=peripheral blood progenitor cell, BMT= bone marrow transplantation*

Administration of filgrastim has been shown to significantly reduce the risk of febrile neutropenia in patients undergoing a chemotherapy that bears a risk of more than 40% to develop febrile neutropenia [41, 42, 44]. In two trials filgrastim administration resulted in a decrease in antibiotic use and hospitalisation [42, 44]. A significant difference in confirmed infections, infectious mortality, response rates or survival between filgrastim and placebo treated patients has not been demonstrated [39, 40].

Bone marrow transplantation (BMT) enables the use of very high doses of chemotherapy to eliminate malignant cells from patients with refractory tumours. Before the bone marrow recovers after transplantation, the neutrophil count usually plunges to zero; filgrastim is indicated to reduce the duration of this neutropenia. Many trials have been performed in this area. Neutrophil recovery is generally enhanced, the incidence of infection is either not affected or lower, and hospital stay is generally not affected or is of shorter duration in G-CSF-treated patients [45].

Peripheral blood progenitor cell (PBPC) transplantation is increasingly applied as an alternative to BMT. Progenitor cells found in the blood can be collected and concentrated for reinfusion after myelosuppressive cancer chemotherapy. Normally the number of progenitor cells circulating in the blood is too low to harvest for transplantation. However, HGFs such as filgrastim expand the population of circulating hematopoietic progenitor cells and may be used to facilitate peripheral collection. PBPC transplantation is attractive, because it is less invasive and technologically complex than BMT. It can be performed in the outpatient setting without anaesthetising the donor. Three randomised trials have shown a difference in favour of PBPC transplantation over BMT, with respect to haematological recovery and hospitalisation [46-48]. There is, however, no evidence that PBPC transplantation significantly improves cancer-free survival rates, the primary goal of PBPC transplantation. Moreover, there might be a risk that the apheresis products

may be contaminated with tumour cells [49]. A recent article in the Lancet reported that high dose chemotherapy supported with PBPC transplantation did not have an effect on tumour recurrence in breast cancer [50].

Filgrastim has recently received approval to treat clinically significant neutropenia in HIV patients during treatment with antiviral and/or other myelosuppressive medications [51].

Amgen is also investigating filgrastim as an adjunct to dose intensified chemotherapy in patients with various tumour types. Moreover, the company is investigating filgrastim's potential benefits for patients in severe infectious disease settings.

### *Cost-benefit/cost-effectiveness/cost-utility*

The use of filgrastim as an adjuvant to chemotherapy, has been calculated to result in savings when the risk of developing febrile neutropenia is greater than 40-50% [43, 52, 53]. If drug wastage is considered as well, the risk has to be higher [43]. Drug wastage may especially be an issue in paediatrics, since dosing is based on weight (i.e. 5µg/kg) and the product is marketed as single dose vials of 300 and 480µg. It remains to be seen if this high risk criterion is met in practice. A Canadian survey determined that on average only 12.3% of new chemotherapy patients develop febrile neutropenia [43]. Based on this number, it was calculated that the use of G-CSF would incur a cost of US\$19,567 per case of febrile neutropenia avoided [43].

In two cost-minimisation analyses comparing PBPC transplantation and autologous BMT, PBPC transplantation resulted in a cost reduction of 15-30% compared to autologous BMT [54, 55].

### *Ethical, legal and social issues*

There does not seem to be great concern in the health care field about unbridled use of filgrastim and associated risks and costs. In fact it has remained remarkably quiet around filgrastim. Large political or public debates and assessment reports are absent.

### **Recombinant human growth hormone**

From 1958 to 1985 pituitary derived growth hormone (pit-hGH) was used as replacement therapy for growth hormone deficient children (Table 3). At that time growth hormone (GH) was scarce and expensive and exploration of other therapeutic applications was not possible. The introduction of recombinant human growth hormone (rhGH) in 1985 coincided with reports of a number of cases of Creutzfeldt-Jakob disease in patients who received pit-hGH in the past. This led to the removal of pit-hGH products from the market. With the large scale production of rhGH, new indications for use could be explored. Besides the use in growth hormone (GH)

deficient children, GH has since 1985 also been registered for use in children with chronic renal insufficiency, children with Turner's syndrome and adults with growth hormone deficiency (GHD). Current dosing schedules consist of daily subcutaneous injections, which are often self administered. The pharmaceutical industry is working on the development of sustained release preparations.

As rhGH exerts a wide scope of actions, many indications like osteoporosis, malnutrition, wasting syndromes, female infertility, wound healing and burns are currently being investigated [56].

### *Safety*

Children are remarkably free of side-effects when they use rhGH. The single concern has been whether children receiving rhGH have an increased risk of developing leukaemia. However, the current consensus is that this is not the case. A shortterm side effect of rhGH administration to adults can be fluid retention and in the long run there may also be an increased cancer risk. No data are available to address this issue, because no adults have received long-term rhGH therapy yet [57].

### *Efficacy/effectiveness*

To determine the effectiveness of rhGH therapy is a very complicated matter. In the first place, it is difficult to distinguish between growth hormone deficiency (GHD) and idiopathic short stature (short stature without an underlying pathology), which is not an approved indication for rhGH treatment. In practice doctors have to work with a continuum of probability of GHD, based on several clinical parameters and tests. Secondly, there is the problem of predicting what the children's untreated height would have been: prediction models and controls both have disadvantages to them. Using controls is difficult because of the numbers of variables to be considered (e.g. age, sex, parental height, bone-age delay, nutrition, and disease and treatment characteristics for Turner's syndrome and renal insufficiency). For the height prediction models, the confidence limits are wide, especially in younger children [58]. Because of the uncertainties in the diagnosis of GHD and in measuring the effect of treatment on final height, it is difficult to apply the results of clinical trials to individual patients.

Untreated, men and women with GHD will reach a height of approximately 140 and 130 cm, respectively. Roughly speaking, rhGH treatment can add 20-30 cm to their final height [59].

Turner's syndrome is a disease of females caused by partial or total loss of one sex chromosome and is characterised by incomplete development of secondary sexual characteristics, infertility and physical abnormalities like short stature (147 cm on average). In the late 1980s, when rhGH was registered for this indication, there was great optimism. However, more recent data, have been relatively disappointing [58].

|             |  |
|-------------|--|
| 1956-1957   | Isolation of human growth hormone from pituitary glands  |
| 1957-1985   | Use of pit-hGH as replacement therapy in GH deficient children   |
| 1979        | Human GH was first cloned  |
| 1982        | First use of rhGH in humans  |
| 1985        | Creutzfeldt-Jakob disease in patients who had received pit-hGH<br>Removal of pit-hGH from the market<br>First marketing authorisation for rhGH to treat hormone inadequacy in children (USA)   |
| 1987 – 1998 | rhGH on European market<br>Registrations for Turner's syndrome, renal insufficiency, and GH deficiency in adults<br>Research for many new indications (diabetes, osteoporosis, fertility problems, total parenteral nutrition, HIV associated wasting) |
| 1997        | Advancement of sustained release preparation to phase III trial  |

*GH=growth hormone, pit-hGH= pituitary-derived human growth hormone, rhGH=recombinant human growth hormone*

In the Netherlands, for example, reimbursement for this indication has recently been suspended because the small increase in final height (3 cm on average) would not justify the costs associated with the treatment.

The group of children with renal insufficiency is a very heterogeneous group. Several variables, like stage of the disease, time of transplantation, dialysis schedule and comedication, could influence the effect of rhGH therapy [56].

GHD in adults is associated with obesity, reduced extracellular water, reduced bone density, increased LDL cholesterol, increased body fat and decreased lean muscle mass and strength [60]. In clinical trials it has been shown that rhGH therapy can reverse these biological changes to varying degrees. However, although rhGH treatment can improve lipid profile and bone density, it has not been shown to have an effect on cardiovascular risk and fracture risk [61-64].

#### *Cost-benefit/cost-effectiveness/cost-utility*

When treating children with rhGH, an improvement of final height is not a goal in itself. The question is, does short stature have a negative influence on the quality of life and, if so, can GH treatment improve this impaired quality of life. Several studies have shown that children with GHD, Turner's syndrome or renal insufficiency remain behind in social and psychological functioning, and have difficulties in finding a partner. For Turner's syndrome and renal insufficiency it is hard to tell what causes these symptoms, because these diseases consist of multiple pathology. Up until now, an objective, measurable improvement of quality of life has not been consistently demonstrated after GH treatment of children [59]. In the vast majority

of studies costs are left out of consideration. Reasons for this might be that GH treatment is regarded as a substitution therapy and an alternative treatment does not exist.

In adults with GHD, quality of life is improved in about 50% of patients receiving GH replacement therapy. It is not known exactly what causes this improved quality of life and how to identify ‘the good responders’ beforehand [61]. It has been argued, however, that economic evaluations of treating GH deficient adults should measure not only quality of life, but also the impact on cardiovascular risk and fracture risk and on disability and early retirement costs [62]. Others have responded to that by noting that there is not enough evidence on which such an evaluation can be based [63].

#### *Ethical, legal and social issues*

rhGH is indicated for conditions that are not life threatening and it is used mostly in a domestic setting. Although the users of rhGH are united in patient organisations, these organisations are too small to exert influence on national policy-making. It seems that rhGH raises much more concern about containing its proper use than other biotechnology drugs. Since it is not easy to make a clear diagnosis in GHD, one might fear that it would be easy to use GH treatment for healthy short children, which is perceived as being unethical by some strong opponents [65]. Also, the non-specific nature of the clinical features experienced by GH deficient adults (obesity, mild depression and fatigue), have made people fear that greater public awareness of the beneficial effects of replacement will lead to ‘media onset GHD’ [61].

### **SYNTHESIS AND COMPARISON OF CASES**

A synthesis of the three cases was made. When looking through the cases we found several issues that have been of importance in all three cases and other issues that were special for one drug and had great impact on its fate. Below we describe the issues that we consider relevant for the assessment and fate of the three cases (Table 4).

#### **Safety**

##### *Previous usage in non-recombinant form*

rhGH is the only product that previously had been used in a non-recombinant form. This means that there was already substantial insight in the therapeutic potential, which there was not for HGFs and nebacumab. Moreover the non-recombinant form is often derived from human material and bears a risk of contamination with micro-organisms.

## Chapter 2

The switch to the recombinant form is usually associated with an improved safety, although this does not necessarily have to be true. Nevertheless this association does constitute an advantage to the biotech drug in question.

### *Species specificity*

High species specificity, as we can see in the nebacumab case, is a great disadvantage, since it restrains the usefulness of animal models. Pharmaceutical companies, and ultimately society, are thus faced with bigger risks when introducing the product in people. Moreover, the absence of a reliable animal model to test the compound's activity may also cause problems with quality assurance [21].

### *Adverse effects*

Obviously, an acceptable safety profile is one of the most important characteristics for a pharmaceutical to be successful. Today's society is very safety driven. Cars, food, toys, domestic appliances etc., all have to comply with strict safety regulations. A pharmaceutical can not afford its safety image to be damaged. In the case of nebacumab, it has been a safety problem, combined with a lack of efficacy, that led to its removal from the market. Although, in this case, one could also consider the safety issue a patient targeting problem, since the problem arose in a group of patients that was not supposed to receive nebacumab in the first place.

### ***Efficacy/effectiveness***

#### *Indication dynamics*

A striking similarity between filgrastim and rhGH, is the growing number of indications over time. Both drugs entered the market registered for one, relatively small and well defined indication. At the present time, however, they possess registrations for four or five additional indications and many clinical studies are under way to evaluate other applications. We labelled this phenomenon 'indication dynamics'. For the industry, of course, it is very attractive to develop additional indications for an existing product, since production facilities, quality assurance procedures, stability data etc. are already in place. The phenomenon of 'indication dynamics' illustrates that pharmaceutical innovation does not have to be a linear process originating from knowledge about a disease. In this case, innovation is prompted by drugs that are 'looking for more diseases' [66]. Filgrastim and rhGH are both eligible candidates to 'look for diseases': neutropenia presents in many different circumstances and GH exerts a very broad range of actions. For nebacumab it would have been more difficult to expand its number of indications.



**Table 4** Comparison of nebacumab, filgrastim and recombinant growth hormone

|  | <b>Nebacumab</b>  | <b>Filgrastim</b>   | <b>Recombinant growth hormone</b>   |
|--|---|---|---|
| <b>Safety</b>                            |   |   |   |
| Previously used in non-recombinant form? | No  | No  | Yes   |
| Species specificity                      | Very species specific<br>Increased mortality in patients without Gram-negative bacteremia (Ziegler: p=0.36; CHES: p=0.09) | Not species specific  | Species specific  |
| Adverse events                           | Increased mortality in patients without Gr.-negative bacteremia   | Medullary bone pain (15-39%)                                      | Remarkable safe. Pain at injection site. Only concern: increased cancer risk. |
| <b>Efficacy/effectiveness</b>            |   |   |   |
| Market entry                             | 1991 (withdrawn '93)  | 1991  | 1985  |
| Use                                      | Therapeutic   | Prophylactic (later therapeutic)                                  | Therapeutic   |
| Indication                               | Disease (bacteremia)  | Therapy-related side-effects (neutropenia caused by chemotherapy) | Disease (growth hormone deficiency)   |
| Therapeutic field                        | Immunology  | Oncology  | Endocrinology   |
| Preclinical data                         | Not robust  | No comments   | No comments   |
| Supplemental indications                 | None  | Many  | Many  |
| Patient targeting                        | Impossible to confirm Gram-negative infection at the start of therapy   | Prophylactic use: no targeting necessary                          | Difficult to diagnose and to assess outcomes                                  |
| Managed entry                            | Issue   | Issue   | Issue   |

**Table 4 continued** Comparison of nebacumab, filgrastim and recombinant growth hormone

|                                   | <b>Nebacumab</b>   | <b>Filgrastim</b>   | <b>Recombinant growth hormone</b>  |
|-----------------------------------|--|---|--|
| <b>Cost/ cost-effectiveness</b>   |  |   |  |
| Hospital/community pharmacy       | Hospital   | Hospital and community pharmacy   | Community pharmacy (prescription from specialists)   |
| Price                             | c. \$3500 (1993) (single dose)                                       | c.\$1500 per cycle (for 10 days)  | \$12 000 -50 000 (per year)  |
| Economic evaluation               | Cost-effectiveness analyses  | Cost-minimisation analyses  | Cost-utility analyses  |
| Outcome                           | Incremental cost per life year saved: c. \$24,100 [34]               | As an adjuvant to chemotherapy: decrease in total hospital costs, if risk >40-50% | Doubtful: improvement of quality of life has not been consistently demonstrated[59]                              |
| Waste                             | No (standard dose)   | Yes   | Possible   |
| <b>Ethical/Legal/Social</b>       |  |   |  |
| Activity of patient organisations | No   | Strong oncology lobby   | Less influential   |
| Ethical issue                     | Yes: because of high costs choices have to be made (hospital budget) | No: filgrastim is perceived as lowering hospital costs                            | Yes: 1) high costs while improvement quality of life has not been proven, 2) danger of treating healthy patients |
| Danger of unwarranted uses        | No   | Yes, indications could be interpreted too broadly                                 | Yes, indications could be interpreted too broadly and abuse in sports  |

### *Managed entry*

While pharmaceutical industries try to expand the field of application of their products, government authorities and third parties are often acting from a cost-containment policy and they try to restrict the use of these products strictly to the approved indications and to patients for whom benefit has been demonstrated. This may be pursued by formulating guidelines for usage or by allowing only designated clinicians, from highly specialised provider units, to prescribe the drug. These methods, of managed entry, have also been applied to filgrastim, rhGH and nebacumab.

### *Effectiveness versus efficacy*

It is not an easy task to decide for which category of patients treatment would be beneficial and to formulate clinical guidelines. Many papers have noticed the difficulty in translating the data from clinical trials into everyday, clinical practice effectiveness [8, 9, 67-69]. Leufkens and Urquhart [70] have described the determinants of drug exposure that influence the safety and effectiveness of drug usage: demographic and socio-economic patient-characteristics, severity of disease, comorbidity, time-schedules of drug-usage, and compliance with therapy. In a clinical trial the variation in these determinants is kept to a minimum, in order to be able to reach sufficient statistical power. Therefore, uncertainties remain about the total effectiveness in general practice and about the efficacy in special subgroups or circumstances. In the cases of filgrastim and rhGH we found many examples of this, sometimes inevitable, lack of knowledge.

### *Intermediate endpoints*

In the cases of both filgrastim and rhGH, little data is available on final clinical endpoints, and therefore intermediate endpoints are often used instead. In literature it has been pointed out that it is necessary to be careful with the usage of surrogate endpoints, since they do not always turn out to be good predictors for the primary outcome of interest [71]. In some cases, however their usage may be inevitable. In the case of rhGH for example, we are confronted with a primary outcome that lies 10-15 years in the future and it would not be beneficial to both industry or patients to keep the product of the market for so long. In today's opinion, we should strive for the usage of clinical endpoints, but if this it not possible, prediction models will be needed to establish the value of certain intermediate outcome measures [72].

### ***Cost-benefit/cost-effectiveness/cost-utility***

The uncertainties about efficacy and effectiveness, make themselves felt in cost-effectiveness studies as well. Moreover, health economics is a relatively young science and methodologies are still being developed and improved [73]. However, cost-effectiveness is becoming increasingly important. At this moment cost-effectiveness evaluation is not yet part of the formal assessment of drugs in most countries (excluding Canada and Australia), but many governments are developing policies to integrate this criterion in their decision-making process in the very near future. When comparing the cases of filgrastim and rhGH, we noticed that the perception of filgrastim as being a cost-saving agent does contribute to its success. Additional indications for rhGH, however, encounter more opposition from government authorities and payers, since they cause substantial increases in the health care budget.

### ***Ethical, legal and social issues***

Besides cost-effectiveness, another reason for the fact that filgrastim encounters less opposition than rhGH, may be that it is used in cancer patients. The lobby for cancer is very strong and few people dare to raise doubts about new therapies in this field. Centocor, the manufacturer of nebacumab, was in a hurry to get nebacumab into the market [25]. Many biotechnology companies are small start-up companies that are under a lot of pressure from their investors to generate returns. In general they will be in a hurry and also they will have difficulties in conducting more than one large clinical trial. Moreover, sometimes early promises are already communicated to society through the media at an early stage of development. This mechanism also increases the pressure on companies to come up with results.

## **DISCUSSION**

By studying three cases of biotechnology drugs, i.e. nebacumab, colony stimulating factors and rhGH, we have evaluated the factors that are important in the assessment and diffusion of such pharmaceuticals. An important question is how the results of the study are affected by the choice of the three cases. The selection of the cases has not been random. The cases have been chosen to cover a broad range of potentially relevant issues. All three cases are different in terms of therapeutic class, origin, time period of introduction, market position, etc. and represent very likely a best available mix of features determining the success or failure of a biotech pharmaceutical. We do realise, however, that factors related to pre-marketing failure of a product might have been missed. Our cases were all products that received marketing authorisation at some point. By studying cases that never reached that point, one could possibly encounter other issues as well. The study has only been based on published literature and written reports.

We did not acquire inside information from the parties involved, e.g. government authorities or industry. Inside information, however, would probably provide valuable additional data to our study and we are considering using that strategy in a further study.

Many issues that determine the fate of a biotechnology drug seem to be similar to those of classical drugs. Only the high costs of a biotechnology drugs and the small number of patients involved generally attract extra attention, which makes these issues more pronounced. The economics of biotech drugs are an important driver of complex adoption processes (reimbursement, formulary decisions, etc.). The relatively small number of patients is an important limiting factor for clinical programs evaluating efficacy, as only small trials are feasible. In cases of pharmaceuticals previously used in a non-recombinant form, i.e. rhGH, this is mostly only a minor issue because efficacy mostly has been previously evaluated. Success factors of biotech drugs in the R&D phase are low species specificity (so that it is possible to develop good animal models), proof of efficacy in a well conducted clinical trial of sufficient size, a good safety profile and the availability of diagnostic tests for easily identifying patients who may benefit from the treatment.

This analysis has shown that the possibility of broadening the range of indications is an important strategy in this class of drugs. In both colony stimulating factors and rhGH, we have seen patterns of indication dynamics. We consider this feature as a key factor to investigate further as it will strongly determine the rationing of the usage and cost containment of these compounds. At the moment other biotech drugs are entering the market with well-defined indications at the beginning, but with a clear tendency of being used and/or approved for other indications as well. A good example is abciximab (ReoPro<sup>®</sup>, a glycoprotein IIb/IIIa inhibitor), that is registered as an adjuvant treatment in addition to heparin and acetylsalicylic acid to prevent ischemic cardiac complications in high-risk patients during percutaneous transluminal coronary angioplasty (PTCA) [74]. Because of its mode of action it is a feasible candidate for off label use and/of approval for other indications (unstable angina and other coronary diseases) in the near future. However, broadening of indications in itself does not have to be negative; it can also be considered an important form of medical innovation. [75] Another related issue concerns the fact that many of these biotechnology compounds, like colony stimulating factors and abciximab, are linked to other intervention strategies like surgery, chemotherapy, percutaneous transluminal angioplasty etc.

A key factor identified in this study is the definition and measurement of clinically relevant outcomes (short and long-term). In all three cases it has been shown that market approval and adoption in clinical practice relies heavily on the appraisal of various clinical, economical and societal outcomes. Recently, Detsky and Redelmeier [76] have put health outcomes and gains in perspective.

## *Chapter 2*

Their comments focus on the misunderstanding of data on health gains by clinicians, policy makers and the public. The trade-off between the costs and benefits in the assessment of drug therapy depends strongly on the appraisal of various outcomes, where facts and values from the perspective of the parties involved may differ [13]. In such circumstances, strong lobbies for or against drug treatment in certain disease categories (e.g. cancer and HIV) emerge. However, society also needs treatments for diseases that do not have a strong lobby and diseases with more problematical outcomes. The current trend towards evidence-based medicine means that we will increasingly have to take decisions based on 'uncertain ' or incomplete' knowledge. The challenge to technology assessment will be to deal with such uncertainties in a sensible way. Only then, it can be a good tool to support medical decision-making.

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## Chapter 2

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# 3

## **Differences in attitudes, knowledge and use of economic evaluations in decision-making in the Netherlands: the Dutch results from the EUROMET project**

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## **ABSTRACT**

*Aim* - To investigate differences in attitudes, knowledge and actual use of economic evaluations in different groups of decision-makers and to compare the results from the Netherlands with the overall results of the European Network on Methodology and Application of Economic Evaluation Techniques (EUROMET) project.

*Methods* - Members of the EUROMET group conducted interviews and surveys with politicians, regulators, hospital pharmacists and physicians in the Netherlands. Three approaches of investigation could be adopted: (i) a postal questionnaire survey, (ii) semi-structured interviews, and (iii) a focus-group approach.

*Results* - In the Netherlands, decision-makers generally have a positive attitude towards economic evaluations. Nevertheless, their actual use and knowledge of economic evaluations are still limited. Hospital pharmacists and regulators are more objective than physicians and politicians, who also base their judgements on other societal values. Hospital pharmacists and regulators have a greater knowledge of economic evaluations, and they use them more often than the other groups. Most decision-makers do not want to base their decisions strictly on a cost-effectiveness ranking alone. Our findings are similar to the findings in other European countries.

*Conclusion* - Decision-makers prefer to make their own broad comparisons of advantages and disadvantages, and do not base their decisions solely on a single summary measure.

## **INTRODUCTION**

As a society, we have mixed feelings about the increasing costs of healthcare [1]. On the one hand, people are concerned about the enormous increase of healthcare expenditures during the past decades. From 1980 until 1995, healthcare expenditures per capita have increased by 300% in Europe [2]. Healthcare, which was equivalent to only 3.8% of the Dutch gross national product (GNP) in 1960, is now at between 8 and 10% GNP [2]. Obviously, these developments raise political concerns, as less money can be spent in other areas. Moreover, employers and employees do not like to spend ever-increasingly on healthcare. Raising taxes and premiums is not acceptable for most stakeholders, and doing so may cause severe economic side effects. Consequently, there is a strong call for cost containment in healthcare.

On the other hand, no matter how high the costs are, or how small or uncertain the benefits, patients generally expect every effort to be made to improve their health. Bringing costs into medical decision-making is often considered to be unethical [3]. These conflicting views are also found with regard to cost-effectiveness analysis (CEA). Advocates of CEA argue that it is the most sensible way to allocate scarce resources, while some opponents are of the opinion that decision-making in healthcare should not be based on costs. Moreover, there is criticism of the techniques used in economic evaluations because some of the methodological and standardisation issues have not been completely resolved.

There is only limited knowledge about the influence of economic evaluation studies on healthcare decision-making. Alban [4,5] and Davies et al.[6] asked researchers from Denmark and ten European Community countries, respectively, about the impact of their work. Only two studies, both in the UK, have surveyed decision-makers rather than researchers: Drummond et al. [7] sent a postal questionnaire survey to pharmacists and directors of public health services; and Duthie et al. [8] used interviews on the relevance of a number of diverse health economic measures. Generally, it was concluded that the impact of economic studies was limited. However, little is known about European countries other than the UK, about the reasons and attitudes behind this possible lack of impact, and about potential differences between different type of decision-makers.

Decision-making about healthcare technologies takes place at different levels. On the macro level, politicians and regulators have to decide, for example, about the licensing and reimbursement of pharmaceuticals. On the intermediate level, decisions are made by specialist organisations (in developing good practice guidelines) and formulary committees. Ultimately, on the micro level, physicians and patients make choices about individual treatments. Since these decision-makers view the process from different perspectives, their attitudes towards economic evaluations as a tool for decision-making may also vary. We conducted interviews and surveys with politicians, regulators, hospital pharmacists, and physicians in the Netherlands

to gain insight into their attitudes, knowledge and use of economic evaluations, and to learn whether differences exist between these groups.

Our second research question arises from our participation in the European Network on Methodology and Application of Economic Evaluation Techniques (EUROMET): do decision-makers in the Netherlands have similar opinions on CEA as their colleagues in other European countries? The EUROMET project aims for the standardisation of methodology in Europe, to enhance the status of economic evaluation. There are eleven project partners from nine European countries (Finland, France, Germany, Norway, Portugal, Spain, Sweden, the Netherlands and the UK). In each of the nine countries, three groups of decision-makers were surveyed: physicians, government agencies and a third group that each participant was free to choose. Three approaches of investigation could be adopted: a postal questionnaire survey, semi-structured interviews, and a focus-group approach.

The healthcare system in the Netherlands consists of a mix of public and private elements. Practically all care is provided through private organisations. The government, on the other hand, exerts influence on the insurance system, on the pricing of care and on the quality of care and patients' rights. The insurance system is partly public and partly private. Since the mid-1980s there has been a slow ongoing shift more towards the market and self-regulation. In hospitals and other healthcare organisations, budgeting systems were already in place, but now the government is extending financial responsibility to insurers as well. Through this measure, the government aims to encourage selective contracting and managed care [9].

At the time of our investigation (late 1998 to early 1999), there were no government regulations on the use of economic evaluations in any decision-making process. While we were performing our interviews, the Ministry of Health, through the Health Insurance Fund Council, was preparing a policy to formally include economic evaluation in the decision-making process for the reimbursement of extramural pharmaceuticals that cannot be clustered into the price reference system. In March 1999, this requirement came into effect. In all other areas, economic evaluations are still not officially required.

In this study, we investigated differences in attitudes, knowledge and actual use of economic evaluations in different groups of decision-makers, and compared the results from the Netherlands with the overall results of the EUROMET project.

### **METHODS**

In the Netherlands, nine opinion-leading physicians involved in the development of therapeutic guidelines, six senior regulators and four politicians, were interviewed about economic evaluations. In addition, fifteen hospital pharmacists were surveyed by postal questionnaire.

### **Interview**

We used the semi-structured interview technique developed by the EUROMET group [10]. The content of the questions is presented in Table 1. Four dimensions of the respondents' position concerning economic evaluation in healthcare were assessed, namely: (i) potential use of economic evaluation and attitudes towards it; (ii) actual use of economic evaluations; (iii) extent of knowledge about economic evaluation; and (iv) potential barriers to the use of economic evaluations.

To assess which criteria decision-makers generally use when assessing new technologies, we started the interviews with a discussion about a hypothetical new drug to treat obesity. We then left this hypothetical scenario and spoke in general about cost-effectiveness as a criterion for decision-making.

Names of opinion-leading physicians were given to us by the National Organisation for Quality Assurance in Hospitals, an organisation that supports the development and implementation of consensus guidelines in the Netherlands. We interviewed physicians from nine different fields of medicine: general practice, internal medicine, dermatology, gynaecology, anaesthesia, neurology, pathology, surgery, and cardiology. The four politicians we interviewed, were the spokespersons for healthcare in parliament for the four largest political parties in the Netherlands. The regulators consisted of three executives of the Health Insurance Fund Council, one executive from the Ministry of Health, one executive of the National Health Council and one executive of the Medicines Evaluation Board.

### **Postal questionnaire**

The fourteen hospital pharmacists surveyed by a postal questionnaire were considered to be either key individuals in Dutch hospital pharmacy or a member of the Efficient Pharmacotherapy Study Group from the Dutch Society for Hospital Pharmacists. Two hospital pharmacists affiliated to our department made this selection. The questionnaire was based on the same format that we used for the semi-structured interviews. The content of the questions is presented in Table 1.

### **Definitions**

Economic evaluation studies were meant to include all formal studies comparing the costs and (if required) consequences of relevant alternatives: cost-minimisation, cost-effectiveness, cost-benefit and cost-utility studies. In the interviews, and in this article, we often used the term 'cost-effectiveness' to encompass each of these different forms of economic evaluation. Healthcare technologies were generally understood to cover all instruments and conditions under which medical practice is exercised. These included drugs, devices, procedures, facilities and the organisational and support systems within which healthcare is delivered. In this study, however, we focused mainly on diagnostic procedures and treatment possibilities.

## RESULTS

The main results of this survey are summarised in Table 1 and depicted in Figure 1.

### ***Criteria for the assessment of healthcare technologies (hypothetical scenario)***

Both the interview and the postal questionnaire began with a hypothetical scenario about the introduction of a new drug to treat obesity that was likely to considerably increase the drug bill in the Netherlands. Respondents were asked about which criteria they would base their judgement on about this drug.

All respondents referred to efficacy and safety, although two politicians used terms like ‘a revolutionary new drug that really works’, without getting into the technical details of how this should be determined. In fact, the Members of Parliament answered that their role in drug assessment was limited. In most cases, Parliament simply accepts the Health Minister’s decision, which is based on advice from the Health Insurance Fund Council. If Parliament interferes with this decision, it tends to become an issue in which politics are more important than the facts. Many physicians, hospital pharmacists and regulators made the efficacy criterion more explicit by using terms such as the therapeutic value as compared with alternative treatments, looking at total outcome, avoiding surrogate endpoints and looking at the long term preventive effect (on morbidity and mortality) or at the improvement of quality of life.

Costs and savings, cost-effectiveness or budgetary impact were mentioned by approximately three out of four respondents. Only a few respondents answered that (i) costs are only of secondary importance, (ii) on the micro level, costs should only be considered when dealing with ‘me-too drugs’, or (iii) the national drug budget should be less rigid, since it now hampers innovation. About one out of four physicians and regulators, and 1 politician (who was also a practising general practitioner) brought up the issue of defining certain subgroups or sub indications for which the treatment might be most cost-effective. Related to this factor is the likelihood of broadening indications, that is, the chance that a product that is registered or reimbursed for a relatively small indication (or subgroup) may subsequently be used in a much wider range of patients. This was of special concern to the regulators. Other criteria that were mentioned once or twice are listed with the type of respondent who brought up the criterion stated in parentheses:

- severity of the disease (regulator, politician)
- burden of treatment for the patient (physician, regulator)
- pharmaceutical quality of the product (regulator)
- amount of experience with the technology (physician, regulator)
- user friendliness of diagnostic equipment (physician)
- whether the technology can be charged to the patient himself (regulator)
- fit with the main areas of attention of the clinic (hospital pharmacist)

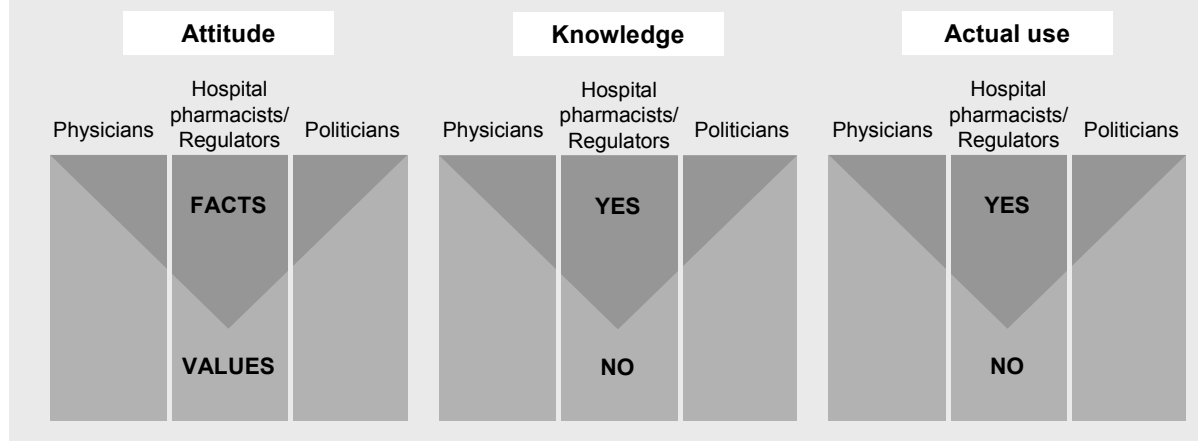


**Table 1** Economic evaluations in healthcare: opinions from physicians, hospital pharmacists, regulators and politicians

| Parameter  | Physicians<br>(n=9)                                   | Hospital<br>pharmacists<br>(n=15)                     | Regulators<br>(n= 6)   | Politicians<br>(n=4)                          |
|--|---|---|--|---|
| <b>Criteria for the assessment of healthcare technologies</b>                                |   |   |  |   |
| What are the most important criteria for the assessment of a new technology?                 | Efficacy and safety, costs, subgroup <sup>a</sup>     | Efficacy and safety, costs                            | Efficacy and safety, costs, Subgroup <sup>a</sup>              | Regulators' advice, costs, and politics       |
| <b>Attitude towards economic evaluations</b>   |   |   |  |   |
| Ethical to refuse treatments for CE reasons?   | Yes (majority)  | Yes (all)   | Yes (majority)   | Yes (n=2) and no (n=2)                        |
| Use an explicit cut-off point for CE?  | Mixed   | Yes (80%)   | Generally no   | Generally no                                  |
| <b>Responsibility for allocative efficiency</b>  |   |   |  |   |
| Who is responsible for allocative efficiency in healthcare: government or the professionals? | Professionals (government facilitating & controlling) | Professionals (government facilitating & controlling) | Government (professionals should mainly worry about good care) | Government (emphasis on technical efficiency) |
| <b>Actual use of economic evaluations</b>  |   |   |  |   |
| Are EAs a requirement for decision-making in your situation?                                 | No (1 yes)  | Not asked   | No   | No  |
| Did you ever use an economic evaluation for decision-making?                                 | Only in consensus committees (majority)               | Yes (some)  | Yes  | No  |
| <b>Knowledge about economic evaluations</b>  |   |   |  |   |
| Education in health economics?   | Little  | Not asked   | Yes (majority)   | Generally not                                 |
| Knowing the difference between a CEA and CEU?  | No  | Yes (majority)  | A few  | No  |

<sup>a</sup> Subgroups or subindications for which treatment might be most cost-effective  
 CE=cost-effectiveness; CEA=cost-effectiveness analysis; CUA=cost-utility analysis;  
 EA= economic evaluation

**Figure 1** Attitudes, knowledge and actual use of economic evaluations a schematic representation of the respondents' answers



### **Attitudes toward economic evaluations**

Both the interview and the postal questionnaire included the question: 'Do you think it is ethical to refuse to adopt or finance a new treatment for cost-effectiveness reasons?'. The majority of respondents answered 'yes' to this question. The arguments against refusing treatments for cost-effectiveness reasons were:

- treatments in terminally ill patients are probably not cost-effective, yet it would be unethical to withhold such treatments (politician)
- it is unethical to refuse treatments since savings can still be achieved from within the healthcare organisation, for example, by lowering specialists' incomes and lowering the marketing costs of the pharmaceutical industry (regulator)
- one should not look at the healthcare sector as only a generator of costs, it is also an environmentally clean sector that generates a lot of employment and social gains (regulator)

Three regulators emphasised that it is most important to critically assess the efficacy of a treatment: They commented that 'whenever a treatment is really effective, it will generally also have a favourable cost-effectiveness ratio'. Furthermore, it was mentioned that before refusing a treatment, one would have to explore all alternatives to try and define subgroups in which the treatment does have an acceptable cost-effectiveness ratio.

The respondents were also asked to what extent they agreed or disagreed with the use of an explicit cut-off point for cost-effectiveness (e.g. €20,000 per life year saved, as used in the Dutch consensus guideline for treating hypercholesterolaemia [11]). The majority of physicians, regulators and politicians were not in favour of the use of an explicit cut-off point for cost-effectiveness. Hospital pharmacists, however, generally

agreed with the use of such a cut-off point. They were of the opinion that this would promote an objective and transparent decision-making process to allocate scarce resources. Regulators and politicians were generally against an explicit cut-off point although two of them did favour a cut-off point, but not for it being the only criterion and not as a sharp and rigid boundary. For two politicians, the idea of summarising the total value of a treatment in one figure was totally new and it aroused a lot of resistance.

The attitudes of physicians towards a cut-off point were varied. One physician recognised that cut-off points are already implicitly used in defining subgroups eligible for certain treatments. Two other physicians, although in favour of an explicit cut-off point, took the view that ultimately the media and political opinion would eventually determine what decisions are taken. Arguments against a cut-off point included:

- the foundation and standardisation of economic evaluations are not yet strong enough, and large margins of uncertainty surround cost-effectiveness ratios (physician, regulator, politician)
- doubts exist about the concept of measuring quality of life and the validity of the quality adjusted life year (physician, regulator, politician)
- discrimination of older and disabled people (regulator)
- for a specific individual, a small health effect can mean a lot in terms of quality of life (e.g. treatment of a small dysfunctioning of a musician's hand) (physician)
- we cannot measure the cost-effectiveness of affectionate care for the elderly; only cure can be assessed, not care (regulator)
- it is an a-historical approach: 'In the middle of the 19th century there appeared not to be enough money for good care for many. Through social battle and co-operation, and not through static bookkeeping, enormous progress has nevertheless been achieved' (regulator)

### ***Responsibility for efficiency in healthcare***

When asked where the responsibility for efficiency in healthcare lies, physicians and hospital pharmacists tended to place it more with the professionals in the field, while regulators and politicians were more inclined to attribute the responsibility to the government. However, most respondents emphasised that professionals and the government should co-operate closely since they both play a part in enhancing efficiency.

Physicians generally stressed that the government should turn to the professionals for the relevant knowledge and for performing clinical studies. The government was ascribed a controlling and facilitatory role.

The government should facilitate and stimulate efficiency policy through financing the development of guidelines and offering instruments such as electronic prescription systems and continuing education possibilities.

Like physicians, the hospital pharmacists also mentioned that the professionals, not the government, have the relevant knowledge, that the government should play a facilitory role, and that the professionals and the government needed to cooperate. Remarkably, 4 out of 6 regulators believed that the professionals in the field should just pay attention to ‘appropriate care’, i.e. the right treatment in the right dosage to the right patient at the right time. This would automatically be the most efficient treatment.

Politicians were more concerned with technical efficiency (‘doing things right’) than with allocative efficiency (‘doing the right things’). To make choices and set priorities between treatments was not a topic on the political agenda. More popular subjects in politics were simplifying existing legislation and the development of relevant criteria to assess the quality of care delivered by healthcare professionals and institutions.

### ***Actual use of economic evaluations***

We asked the physicians, regulators and politicians if economic studies are a formal requirement for decision-making in their situation. Only one physician answered ‘yes’, while all of the other respondents said ‘no’. Several respondents noted that good studies were often lacking. This question was not included in the questionnaire that was sent to the hospital pharmacists.

We then asked the participants (including hospital pharmacists) if they had ever used an economic evaluation for decision-making. Five physicians had used economic evaluations while working within consensus committees developing good practice guidelines. One physician had used an economic evaluation to convince a hospital’s management of the advantages of a pre-surgery clinic to perform the necessary examinations before a patient can undergo surgery. The physicians never used economic evaluations to support decisions in the individual patient setting. About one third of the hospital pharmacists and all but one regulator had ever used an economic for decision-making. One out of the four politicians said that he had used economic evaluations for decision-making in healthcare, although he could not come up with an example.

### ***Extent of knowledge about economic evaluations***

Both in the interview and in the postal questionnaire, respondents were asked if they had had any formal training in health economics. Only one physician participated in a one-day retraining course on pharmacoeconomics for physicians. Two physicians said they learned about economic evaluations in healthcare through self-education, one of whom is now actually teaching health economics courses.

In the group of regulators, most of the respondents had had some training in health economics. One of them went to an extensive three-week course. A politician who is a practising family doctor went to a one-day retraining course for physicians. The question about education was not included in the questionnaire for hospital pharmacists since it is normal practice within this group of professionals to attend courses on pharmacoeconomics on a regular basis.

We also asked politicians, regulators and physicians if they knew the difference between a CEA and cost-utility analysis (CUA) and, if so, which type of analysis they preferred. In the postal questionnaire for hospital pharmacists, this question was slightly altered since we expected the hospital pharmacists to be more knowledgeable about this subject. The revised question read, 'Are you familiar with the techniques of cost-minimisation analyses (CMAs), costs-benefit analyses (CBAs), CEAs and CUAs? Which type of analysis is the most useful to you?'

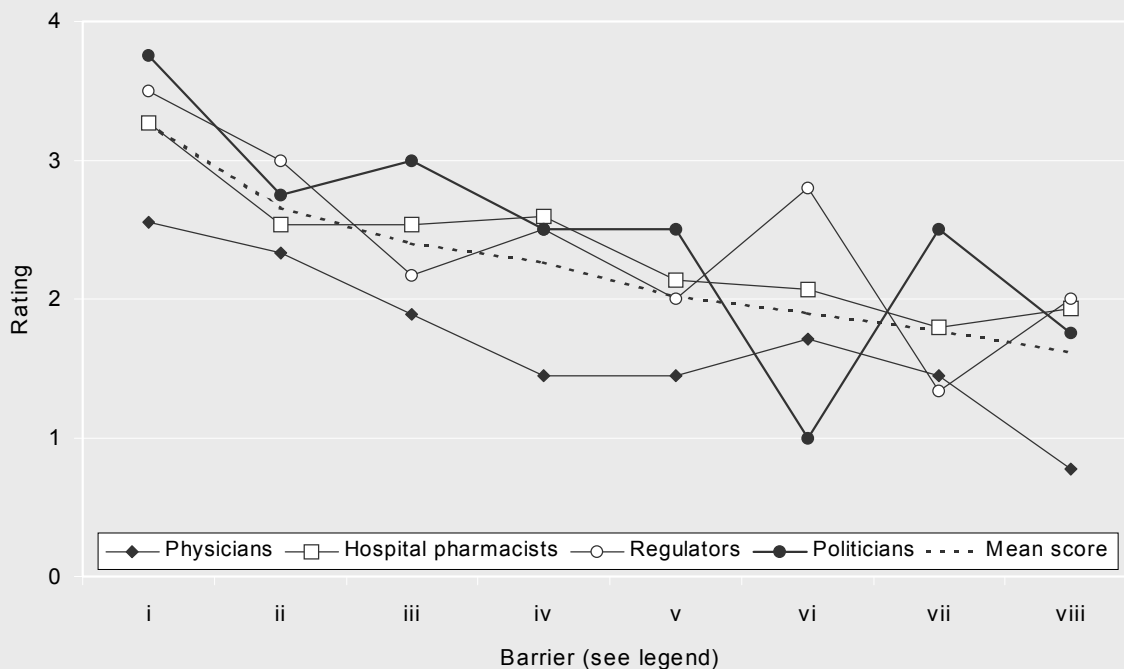
Neither the physicians nor the politicians knew enough about the differences between CEA and CUA to state the advantages and disadvantages of these methods. Two regulators knew the difference between the two methods. They identified the ability to compare treatments for different diseases as an advantage of the CUA, while abstraction from the actual disorder, difficulties in valuing quality of life, and the question of whose values should be used were named as disadvantages. In the group of hospital pharmacists, twelve out of fifteen respondents answered that they were familiar with these different types of analyses. Their preference was equally distributed between CMA, CBA and CEA. CUA was the least popular method.

### ***Barriers to the use of economic evaluations***

Respondents were asked to rate the importance of a list of potential barriers to the use of economic evaluations on a 5-points scale: from 'not important at all' (0) to 'very important' (4). Participants could also add other barriers they felt were missing from our list. The average ratings for the barriers are presented in Figure 2.

The difficulty of moving resources from one budget to another, the fact that cost-effectiveness in real practice can be very different from that predicted in a clinical trial (efficacy versus effectiveness), and economic evaluations making too many assumptions were viewed as the most important barriers by all four groups of respondents. Different views existed between the regulators and politicians with regard to cost containment and the fact that the studies are complicated and hard to understand. Regulators considered cost containment much more important than politicians did. Politicians, in particular, considered economic studies to be complicated and hard to understand.

**Figure 2** Ratings of the importance of eight potential barriers to the use of economic evaluations opinions from physicians, hospital pharmacists, regulators and politicians, and mean score of the 4 groups



(i) Difficulty in moving resources from one sector/budget to another; (ii) Cost-effectiveness in real practice can be very different than predicted from a clinical trial (efficacy versus effectiveness); (iii) Economic studies make to many assumptions; (iv) Sponsorship of studies, e.g. by industry, biases the results; (v) Savings in economic studies are anticipated not real; empty beds are filled again; (vi) Cost containment is more important than cost-effectiveness; (vii) Studies are complicated and hard to understand; (viii) Economic studies are not required in the Netherlands

Potential barriers to the use of economic evaluations that were added to our list by the respondents included:

- economic evaluations are not accepted as a tool by the medical profession (physician)
- economic evaluations discriminate against the ‘non-productive’ population and against people with a lower starting utility, e.g. chronically ill or (mentally) disabled people (regulator)
- there is a lack of available economic evaluation studies (hospital pharmacist)
- many resources and time required to perform an economic evaluation (regulator)

A number of methodological arguments against the use of economic evaluations were also received:

- difficulties in determining the efficacy of treatments, especially in the care sector (regulator)
- difficulties with international comparability (regulators, hospital pharmacist)
- lack of detailed information on care consumption and quality of life scores (physician)
- too much unfamiliarity with new drugs: modelling ignores sudden adverse events that may occur (hospital pharmacist)
- there are no 'good practice guidelines' for economic evaluation studies (regulator, hospital pharmacist)
- difficulties in determining the overhead costs: often too few costs are included (physician)
- difficulties in handling indirect costs (regulator)

### ***Comparison with other European countries***

The combined analysis of the results from all of the participating countries revealed that decision-makers generally have a positive attitude towards and interest in economic evaluations. About 75% of all decision-makers felt that economic considerations should be taken into account, at least to some extent. Approximately, 20% thought that efficiency considerations were very important. The respondents judged ethical issues very differently. Most of the British and Spanish respondents thought that it is ethical to refuse to adopt or to finance a new treatment for cost-effectiveness reasons, whereas only 2% of the Portuguese respondents took this view. In general, most decision-makers did not want to adopt a strict attitude and stated that the refusal might not be based on economic reasoning alone. The actual use of economic evaluation studies in decision-making processes is still limited. At most, a third of respondents across all of the countries stated that they have ever actually used an economic evaluation study. Furthermore, the majority of respondents had only poor knowledge of economic evaluation. Overall, a low percentage of respondents had undergone training in health economics; approximately one third had participated in health economics courses [10].

## **DISCUSSION**

Safety, efficacy, cost-effectiveness, the definition of relevant outcome measures and subgroups, the likelihood of broadening of indications, and politics are important factors in the assessment of healthcare technologies in the Netherlands. Generally, decision-makers have a positive attitude towards economic evaluations in healthcare. However, most decision-makers do not want to adopt a strict attitude and they state that decisions may not be based on economic reasoning alone.

The actual use of economic evaluation, and knowledge about it, are still limited. These observations correspond with findings in other European countries. In the Netherlands, hospital pharmacists and regulators use economic evaluations more frequently, and have more knowledge about them than physicians and politicians. In developing guidelines, consensus committees of physicians sometimes use economic evaluations; in an individual patient setting, however, they do not. Politicians are more concerned with technical efficiency than with allocative efficiency.

The results from the hospital pharmacists were obtained through a postal questionnaire survey, while the other data were obtained using semi-structured interviews. This may weaken the comparability of the results. In general, interviews are likely to be a superior method to mailed questionnaires in situations where: (i) the respondent is unlikely to answer a mailed questionnaire, (ii) the number of respondents is small, (iii) the data required are (mainly) qualitative in nature, and (iv) the researcher does not have a previous clear understanding of the issues nor of the likely responses. When we started the research with the physicians, regulators and politicians, this was generally the case; the number of regulators and politicians we considered it relevant to include was small and they were unlikely to respond to a postal questionnaire. Moreover, since little research had so far been performed in this area in the Netherlands, we had insufficient prior information to develop a valid postal questionnaire.

During the interviews, our opinion was confirmed that it was necessary to speak directly to the respondents to get a good understanding of their views. With the hospital pharmacists, however, the situation was different, in that: (i) a larger group could be easily contacted; (ii) we were more confident that they would respond to a postal questionnaire since they belonged to the same professional group as the investigators; and (iii) by that time, we had enough experience to formulate the appropriate questions, since we conducted the interviews with the other groups first. Indeed, after a reminder by phone, the response to the postal questionnaire was 100% and, as was anticipated, hospital pharmacists were shown to have enough insight into the field of economic evaluations to fill in the questionnaire properly. Therefore, we believe that the methods used were appropriate and that they do not seriously hamper comparability.

Although decision-makers generally have a positive attitude toward economic evaluations, they also criticise them. In an article series in the *Journal of the American Medical Association*, Eddy [12] mentioned that misunderstanding is an important factor in this criticism. He stated that many people have never attended a simple presentation about the fundamentals of healthcare rationing according to cost-effectiveness ratios. We can indeed conclude that all of the decision-makers in the Netherlands do not know the principles of economic evaluations. For instance, neither the physicians nor the members of parliament knew enough about the



differences between cost-effectiveness analysis and cost-utility analysis to name the advantages and disadvantages of these methods.

There are other factors, as well as misunderstanding, that can cause controversy, which Eddy [12] groups into different categories. We would like to modify and extend these categories, based on the arguments we encountered during our interviews and survey (see Table 2). The first category consists of methodological issues, for which we can identify many arguments that were provided by our respondents, namely the absence of a good practice guideline, difficulties in measuring quality of life, and difficulties in determining and measuring all of the relevant costs, etc.

Furthermore, there are clinical arguments against cost-effectiveness reasoning. The main clinical argument is that the results from a cost-effectiveness analysis are often counter-intuitive. For example, in a ranking based on efficiency drawn up by the Oregon Health Services Commission, tooth caps were ranked ahead of surgery for ectopic pregnancy [1]. This reluctance to strictly follow cost-utility league tables also emerged in our interviews.

There is also a group that consists of psychological arguments. Initially, the field of economic evaluation may, by itself, cause scepticism because it is relatively new field of medicine. It utilises a lot of mathematics and abstract thinking, which not all decision-makers are familiar with and which makes it difficult for them to assess the validity of the conclusions. Also, territorial feelings may play a part. Decisions that used to be the practitioners' private domain must now be shared; providers of relatively inefficient care services may feel especially threatened.

Another group of arguments has a more philosophical/ethical character. One philosophical question is, which perspective is the correct one: the practitioner's perspective, which focuses on an individual patient, or the population perspective, which tries to maximise the health of the entire population of patients? Another philosophical problem is the disagreement about whether resources are truly limited. Both questions recurred in the interviews we conducted.

Even if people are willing to accept cost-effectiveness as a tool for decision-making, some practical issues may arise. Several of our respondents felt that good studies are often lacking. The difficulty in moving resources from one budget to another also hampers the implementation of economic studies in the decision-making process.

## **CONCLUSION**

Hospital pharmacists and regulators are the groups most likely to base their judgements on scientific evidence alone, that is, they are more fact oriented than physicians and politicians. Since they do not have to face individual patients or voters, they may take less account of feelings that exist in the general population, political strategies and other contextual factors (values).

**Table 2** Summary of the barriers encountered in the use of economic evaluations, based on Eddy [12] and modified and extended using the findings from our research

| Methodological                                | Clinical  | Psychological   | Philosophical / ethical   | Practical  |
|---|---|---|---|--|
| Difficult to quantify the health benefits     | Results are often counter-intuitive                                   | Saving an identifiable patient is more desirable than preventing anonymous deaths | Pain treatment in terminally ill patients: unfavourable cost-effectiveness but unethical to withhold    | Difficult to move resources from one budget to another |
| There is no 'good practice guideline'         | A treatment that really is effective is generally also cost-effective | Scepticism because the field is relatively new to medicine                        | Discrimination against older and disabled people  | Not enough studies are available                       |
| Difficult to calculate costs                  | For an individual patient a small health benefit can mean a lot       | It requires a lot of mathematics and abstract thinking                            | Doubts about whether resources are really limited   |  |
| Difficulties with international comparability |   | Territorial feelings <sup>a</sup>   | Which perspective is the correct one: the individual patient perspective or the population perspective? |  |
|   |   | Political emotions have an important influence on decision-making                 |   |  |

<sup>a</sup> Providers of relatively inefficient care services may feel threatened.

For individual physicians and politicians, these values play a more integral part in decision-making. Is it necessarily a bad thing that some decision-makers do not base their decisions on scientific facts alone, but take into account humanitarian values as well?

Economists teach that priority setting should take place according to league tables of cost-effectiveness ratios if the dominant objective is to maximise the health benefits that are generated by the scarce resources that are available for healthcare. From our interviews, however, it is clear that many of the respondents were reluctant to base their decisions on cost-effectiveness ratios alone. Concerns about the severity of illness, reluctance to discriminate against patients that happen to have less potential to benefit from treatment than others, territorial feelings and political deliberations, can add to the quality of decision-making. Moreover, it would be an illusion to think that we can succeed in eliminating these factors from the decision-making process.

Should we then try to incorporate broader societal values into economic evaluations? Some health economists are working on incorporating equity concerns into cost-utility analyses [13,14]. We are of the opinion that this will not increase the impact of economic evaluations. Generally, people do not want the solutions to complicated problems to be summed up in single numbers [15]. When registration authorities like the US Food and Drug Administration and European Medicines Evaluation Board assess the balance between the positive effects and adverse events of a new drug, they do not abstract these diverse characteristics into a single number, which is then to be compared with a fixed cut-off point. Rather, they choose to make their own judgements based on perceived benefits and losses. The more factors that become included in cost-effectiveness ratios, the less transparent and comprehensible these ratios will become, and the less likely that people will accept them as being valuable information.

In summary, the impact of cost-effectiveness data may increase through education of the decision-makers and through keeping the calculations transparent and understandable. However, we must not expect decisions to be based on cost-effectiveness ratios alone. Decision-makers prefer to weight a broad range of advantages and disadvantages in their own minds, and not base their decisions on a single summary measure alone. This may also be of importance to the present debate in the Netherlands regarding how to integrate the pharmacoeconomic guidelines that have recently been approved into the assessment procedure for reimbursement [16].

## **ACKNOWLEDGEMENTS**

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# 4

## **Cost-efficacy in interventional cardiology: results from the EPISTENT study**

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## ABSTRACT

*Aim* - The EPISTENT study has demonstrated that the combined use of abciximab and stenting as an adjunct to PTCA leads to increased event-free survival compared to either using abciximab or stenting alone. However, this combined strategy may be costly and the additional costs have to be weighted against the additional effects.

*Methods and results* - The 6-months efficacy data from the EPISTENT study are combined with Dutch estimates of unit costs. Adding a stent to a procedure with abciximab, further decreases the number of revascularisations at an extra cost of €12,000 (95% upper limit (u.l.) € 31,00) per additional major adverse cardiac event-free (MACE-free) survivor. Adding abciximab to a stenting procedure, decreases the incidence of myocardial infarctions at an extra cost of at €13,000 (95% u.l. €27,000) per additional myocardial infarction-free survivor. In the subgroup of diabetics, adding abciximab improves revascularisation rates as well, resulting in a cost-efficacy rate of €2,000 (95% u.l. €25,000) per additional MACE-free survivor, with uncertainty regions indicating potential costs savings.

*Conclusion* - The combination of stenting and abciximab costs about €13,000 to avoid one event after PTCA. In diabetic patients the strategy may be cost saving.

## **INTRODUCTION**

Over the last decade at least two technologies have changed the face of interventional cardiology. First, intracoronary stents, which have been shown to reduce the need for repeat revascularisations by 20-50% [1-7]. Second, the GP IIb/IIIa receptor blockers, most notably abciximab (ReoPro®), which have been shown to be effective in reducing the rate of myocardial infarction and the necessity for urgent revascularisation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) [8-11]. Both technologies are now common practice, stents probably more than abciximab, as in most American and European institutions 60-90% of all angioplasty cases now involve stent implantation [12].

Given the 'separate' effects of stenting and abciximab – stents on revascularisation-free and abciximab on myocardial infarction-free survival – the question that needed to be addressed was whether their combination would lead to a synergistic effect. This was done in the 'Evaluation of Platelet IIb/IIIa Inhibitor For Stenting Trial (EPISTENT)' study [13,14]. Here, three treatments were compared: (1) elective stenting and placebo, (2) elective stenting and abciximab, and (3) balloon angioplasty with abciximab. The combined use of stents and abciximab turned out to be the superior treatment showing both an effect on myocardial infarctions and early re-PTCAs due to the use of abciximab, and effects on late revascularisations due to the use of stents.

Nowadays, the fact that the combination of stents with abciximab has been shown to lead to a significant improvement in event-free survival, or even survival, is not a guarantee for widespread use. Many hospitals, especially European hospitals, face budgetary constraints and the use of stents plus abciximab is associated with additional costs. In these cases, questions may be raised about the balance between the additional costs and the additional efficacy. Additionally, when assessing this balance, the question may not only be whether to treat patients with this combination, but also whom to treat. As such, finding that the combination of stenting and abciximab proved to be especially valuable in diabetic patients was important [15]. Diabetes is an important determinant of restenosis and the need for revascularisations after conventional PTCA. In a subgroup analysis of EPISTENT, however, diabetics in the stent-abciximab group had a similar target revascularisation rate after 6 months compared with non-diabetic patients in the same group. In the diabetic cohort, there was a >50% reduction in the 6-month target revascularisation rate for the stent-abciximab group compared to the stent-placebo group, while in the non-diabetics this reduction was <3%.

Here, we address the question on the balance between the costs and effects of combined use of abciximab and stenting using the 6-months efficacy data from the EPISTENT study, in combination with Dutch estimates of unit costs. We assess both the cost-efficacy of adding a stent to a procedure where the use of abciximab is

planned, as well as the cost-efficacy of adding abciximab to a procedure where the use of a stent is planned. Special attention is given to the uncertainties surrounding the estimates, especially when breaking down the results between diabetics and non-diabetics.

### **METHODS**

The presented analysis can be labelled as a cost-efficacy analysis from a societal perspective in which only direct medical costs are taken into account. The analysis is based on individual data per patient with a time horizon of six months. The analysis includes a subgroup analysis considering diabetic and non-diabetic patients.

#### ***The EPISTENT study***

In the EPISTENT trial 2,399 patients (75% males, aged  $60 \pm 11$  years) were enrolled at 63 hospitals in the U.S.A. and Canada between July 1996 and September 1997 [13]. All patients had ischaemic heart disease and coronary artery lesions that had caused stenosis of at least 60%, amenable to balloon angioplasty or stenting. Patients were randomly assigned to stenting and placebo ( $n=809$ ), stenting plus abciximab ( $n=794$ ), or balloon angioplasty plus abciximab ( $n=796$ ). The primary endpoint of the trial included any of the following events over the first 30 days after randomisation: death from any cause, myocardial infarction or reinfarction, or severe myocardial ischaemia requiring urgent coronary artery bypass surgery, stent placement or PTCA. Further details have been published elsewhere [13].

#### ***Efficacy***

The analysis of cost-efficacy starts with the assumption that the results from the EPISTENT study can be extrapolated to Europe. The clinical endpoint used in the EPISTENT trial and in three other large trials that have been conducted with abciximab, was 'event-free survival', including death, myocardial infarction and urgent revascularisations as events. From an economic perspective, there are various reasons why this outcome may be subject to criticism. Using this composite endpoint, a repeat PTCA receives the same weight as a myocardial infarction, and a myocardial infarction has the same weight as dying. Moreover, revascularisations – even 'urgent' revascularisations – may be subject to clinicians' decisions. Ideally, one would want to use the number of Quality Adjusted Life Years (QALYs) gained through the use of abciximab. However, no data on the quality of life of the study population has been collected. Therefore, we followed the same approach as followed earlier in cost-efficacy studies with abciximab and stenting using two definitions of 'event-free survival'. The first is defined as the percentage of patients surviving 6 months without a myocardial infarction ('myocardial infarction-free survival'); the second is defined as the percentage of patients surviving 6 months with neither a myocardial



infarction nor a revascularisation procedure (major adverse cardiac event-free survival or 'MACE-free survival'). It is noted that we include the urgent as well as the non-urgent revascularisations as events. As such, 'event-free survival' is used as the measure of efficacy, since all events that are included in the definition are very likely to be associated with quality of life and survival probabilities. Also, the various components do not change in opposite directions (in the sense that the use of abciximab would, for example, lead to fewer revascularisations but more deaths). Differences in effects are tested using the Chi-square test.

### **Costs**

Costs are calculated by multiplying the number of events recorded in the trial database by the estimates of costs per event. The estimates of these unit costs are based on the economic evaluation study from the BENESTENT II trial [5].

The costs of initial stenting procedures, including an average number of hospital days, are estimated higher than the costs for initial PTCA procedures. This difference results from the price of the stent, the use of additional balloons and other devices, and a slightly longer duration of the procedure [16]. The costs of the initial procedures are complemented with the costs of abciximab (blinded and open use), the costs associated with bail-out stent implantation, and the costs associated with additional stents.

During the follow-up period, the costs take into consideration open abciximab usage, revascularisations and the resources associated with myocardial infarctions. We estimated that patients experiencing a Q wave myocardial infarction required hospitalisation for 2 days at a coronary care unit (CCU) and another 6 days at a normal care unit. For non-Q wave myocardial infarction patients, we estimated half a CCU day plus half a day at a normal care unit. The costs for a re-PTCA or a repeat stent procedure are estimated higher than the costs for the initial procedures. While the latter does not include the costs for diagnostic procedures (visits, tests, and angiography), the first do. All costs are expressed in 1998 Euros. Differences in costs are tested using oneway ANOVA and contrasts.

### **Cost-efficacy**

The balance between costs and effects is addressed by computing incremental cost-efficacy ratios, i.e. the additional costs per additional event-free survivor. We assess the cost-efficacy of adding stents to a procedure with abciximab by a comparison of the stent plus abciximab arm with the PTCA plus abciximab arm. The cost efficacy of adding abciximab to a stent procedure is assessed by a comparison between the stent plus abciximab arm and the stent plus placebo arm. Additionally, as in the clinical report about efficacy, a breakdown is presented distinguishing between diabetes and non-diabetes patients. The uncertainties surrounding the estimates are addressed by

way of probability ellipses and by presenting upper 95% limits to the cost-efficacy ratios [17]. It is noted that the trial did not include any European patients and that the results are conditional on the assumption that the clinical findings can be extrapolated to a European context.

## RESULTS

### *Efficacy*

The results for all patients confirm that the main effect of abciximab on myocardial infarctions is mainly during the first month, and the main effect of stenting on the number of revascularisations is mainly after the first month. After 1 month, only 45 patients had either died or experienced a myocardial infarction after combined therapy, compared to 90 patients in the stent+placebo arm and 54 patients in the PTCA+abciximab arm. The number of revascularisations during the first month was 25 in the combined arm, 42 in the stent+placebo arm, and 41 in the PTCA+abciximab arm. The additional number of patients who either died or experienced a myocardial infarction during the subsequent months was six in the combined arm, 10 in the stent+placebo arm, and 15 in the PTCA+abciximab arm. The additional number of revascularisations during the subsequent months was 66 in the combined arm, 66 in the stent+placebo arm, and 98 in the PTCA+abciximab arm.

As such, a combination stenting and abciximab leads to significant improvement in efficacy, when compared with a procedure with stent implantation and when compared to a procedure with abciximab. The results in terms of survival, myocardial infarction-free survival and MACE-free survival are presented in Table 1.

The results – not using abciximab – confirm that stenting is associated with lower MACE-free survival in diabetics when compared to non-diabetics (73% vs. 80%,  $p=0.07$ ). However, it appears that when abciximab is used, MACE-free survival after stenting is approximately equal for diabetics and non-diabetics. Thus, in diabetics the use of abciximab not only decreases the numbers of myocardial infarctions – as it does in non-diabetic patients – but it decreases the number of revascularisations as well, suggesting not only an additional effect to stent implantation but also a synergistic effect.

### *Costs*

Table 2 presents the estimates of the average cost per patient for the different contributing factors after 6 months of treatment. The results differ slightly from those that would be obtained by simply multiplying the volumes with the unit costs. This is related to the fact that when two events were observed for one patient, this contributed only once to the efficacy measure, but twice to the costs.

**Table 1** Efficacy at 1 month and 6 months for all patients, non-diabetics and diabetics

|                      | <b>Stent + placebo</b> | <b>Stent + abciximab</b> | <b>PTCA + abciximab</b> | <b>p-value when adding: abciximab stenting</b> |        |
|----------------------|------------------------|--------------------------|-------------------------|--|--------|
| <b>All patients</b>  |                        |                          |                         |  |        |
| N                    | 809                    | 794                      | 796                     |  |        |
| Survival             |                        |                          |                         |  |        |
| 1 month              | 99.38%                 | 99.62%                   | 99.25%                  | 0.50   | 0.32   |
| 6 months             | 98.76%                 | 99.50%                   | 98.24%                  | 0.19   | 0.02   |
| MI-free survival     |                        |                          |                         |  |        |
| 1 month              | 88.88%                 | 94.33%                   | 93.22%                  | <0.001   | 0.36   |
| 6 months             | 87.64%                 | 93.58%                   | 91.33%                  | <0.001   | 0.09   |
| MACE-free survival   |                        |                          |                         |  |        |
| 1 month              | 85.78%                 | 92.32%                   | 89.32%                  | <0.001   | 0.04   |
| 6 months             | 78.37%                 | 83.75%                   | 76.51%                  | 0.006  | <0.001 |
| <b>Non-diabetics</b> |                        |                          |                         |  |        |
| N                    | 636                    | 632                      | 640                     |  |        |
| Survival             |                        |                          |                         |  |        |
| 1 month              | 99.69%                 | 99.68%                   | 99.22%                  | 0.99   | 0.26   |
| 6 months             | 98.90%                 | 99.53%                   | 98.13%                  | 0.21   | 0.02   |
| MI-free survival     |                        |                          |                         |  |        |
| 1 month              | 89.15%                 | 94.30%                   | 92.81%                  | <0.001   | 0.28   |
| 6 months             | 87.74%                 | 93.51%                   | 91.25%                  | <0.001   | 0.13   |
| MACE-free survival   |                        |                          |                         |  |        |
| 1 month              | 86.32%                 | 92.09%                   | 88.28%                  | <0.001   | 0.02   |
| 6 months             | 79.72%                 | 83.54%                   | 76.72%                  | 0.08   | <0.01  |
| <b>Diabetics</b>     |                        |                          |                         |  |        |
| N                    | 173                    | 162                      | 156                     |  |        |
| Survival             |                        |                          |                         |  |        |
| 1 month              | 98.27%                 | 99.38%                   | 99.36%                  | 0.35   | 0.98   |
| 6 months             | 98.27%                 | 99.38%                   | 98.72%                  | 0.35   | 0.54   |
| MI-free survival     |                        |                          |                         |  |        |
| 1 month              | 87.86%                 | 94.44%                   | 94.87%                  | 0.04   | 0.87   |
| 6 months             | 87.28%                 | 93.83%                   | 91.67%                  | 0.04   | 0.46   |
| MACE-free survival   |                        |                          |                         |  |        |
| 1 month              | 83.82%                 | 93.21%                   | 93.59%                  | <0.01  | 0.89   |
| 6 months             | 73.41%                 | 84.57%                   | 75.64%                  | 0.01   | <0.05  |

PTCA=percutaneous transluminal coronary angioplasty; MI=myocardial infarction; MACE=major adverse cardiac event

**Table 2** Costs after six months for all patients

|                           | Incidence of events    |                          |                         | Unit costs (€)  | Costs per patient (€)  |                          |                         |
|---------------------------|------------------------|--------------------------|-------------------------|-----------------|------------------------|--------------------------|-------------------------|
|                           | Stent/<br>place-<br>bo | Stent/<br>Abcixi-<br>mab | PTCA/<br>Abcixi-<br>mab |                 | Stent/<br>Place-<br>bo | Stent/<br>abcixi-<br>mab | PTCA/<br>abcixi-<br>mab |
| <b>Initial procedure</b>  |                        |                          |                         |                 |                        |                          |                         |
| PTCA / stenting           | 98.5%                  | 98.7%                    | 98.6%                   | 4,505/<br>5,904 | 5,816                  | 5,829                    | 4,442                   |
| Bail out stenting         | 0.00%                  | 0.00%                    | 18.3%                   | 2,211           | 0                      | 0                        | 406                     |
| Additional stents         | 0.38                   | 0.30                     | 0.00                    | 1,397           | 527                    | 419                      | 0                       |
| Vials abciximab           | 0                      | 3.23                     | 3.23                    | 347             | 0                      | 1,122                    | 1,122                   |
| Open abciximab            | 1.85%                  | 0.38%                    | 0.25%                   | 1,121           | 21                     | 4                        | 3                       |
|                           |                        |                          |                         |                 | 6,363                  | 7,375                    | 5,972                   |
| <b>Follow-up</b>          |                        |                          |                         |                 |                        |                          |                         |
| Open abciximab            | 1.40%                  | 1.12%                    | 1.01%                   | 1,121           | 15                     | 13                       | 11                      |
| Q wave MI                 | 1.85%                  | 1.64%                    | 2.51%                   | 4,753           | 88                     | 78                       | 131                     |
| Non-Q wave MI             | 9.39%                  | 4.41%                    | 4.90%                   | 719             | 68                     | 33                       | 36                      |
| Re-PTCA                   | 6.30%                  | 4.79%                    | 4.15%                   | 7,178           | 497                    | 380                      | 325                     |
| Re-Stent                  | 4.45%                  | 3.78%                    | 11.3%                   | 7,678           | 361                    | 309                      | 916                     |
| Re-Bypass                 | 4.57%                  | 4.28%                    | 3.89%                   | 17,795          | 814                    | 784                      | 693                     |
|                           |                        |                          |                         |                 | 1,843                  | 1,597                    | 2,113                   |
| Average costs per patient |                        |                          |                         |                 | 8,207                  | 8,971*                   | 8,085                   |

\* Compared to stent/placebo  $p=0.003$ , compared to PTCA/abciximab  $p<0.001$   
PTCA=percutaneous transluminal coronary angioplasty; MI=myocardial infarction

It is noted that 6 months after the initial procedure, 29% of the patients who were not planned to have a stent implanted had indeed received a stent, either by bail-out (18%) or during follow-up (11%).

The combination of both stenting and abciximab administration leads to higher costs for the initial procedure when compared to a procedure where only stenting or abciximab is used. However, a substantial part of the additional costs are compensated for by savings as a result of a decrease in revascularisation procedures and myocardial infarctions. After 6 months, the net costs of adding abciximab to a stent procedure were estimated at €764, after an initial increase of €1,012. After 6 months, the net costs of adding a stent to a procedure with abciximab were estimated at €886, after an initial increase of €1,403.

**Table 3** Incremental cost-efficacy ratios at 6 months for all patients, non-diabetics and diabetics

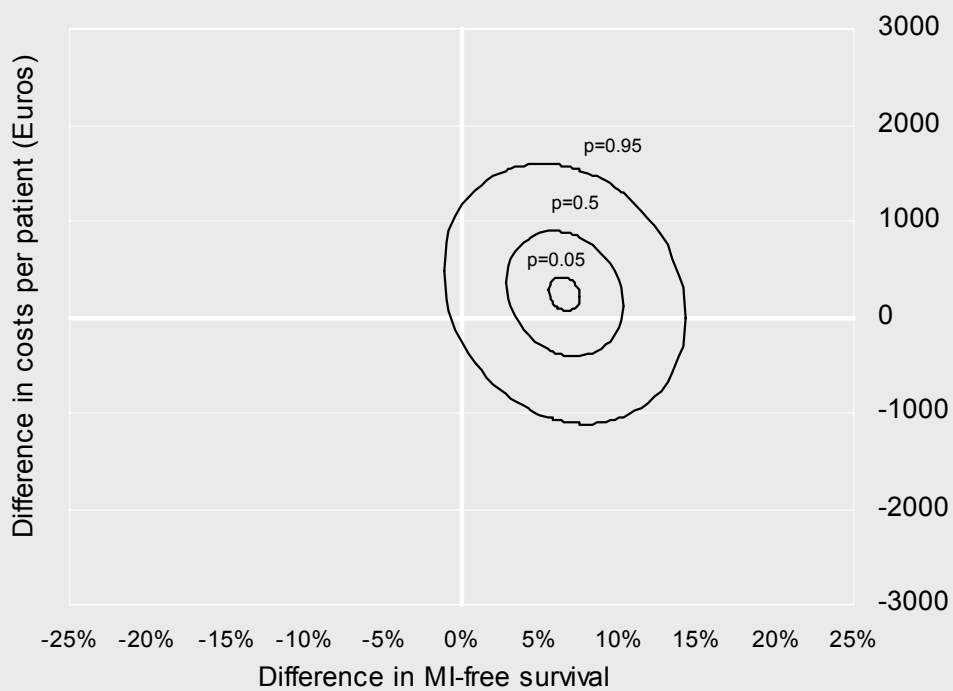
|                      | Stent /<br>placebo  | Stent /<br>abciximab  | PTCA /<br>abciximab |
|----------------------|---|---|---------------------|
| <b>All patients</b>  |   |   |                     |
| N                    | 809   | 764   | 796                 |
| Costs (€)            | 8,207   | 8,971   | 8,085               |
| MI-free survivors    | 87.64 %   | 93.58 %   | 91.33 %             |
| MACE-free survivors  | 78.37 %   | 83.75 %   | 76.51 %             |
| <b>No-diabetics</b>  |   |   |                     |
| N                    | 636   | 632   | 640                 |
| Costs (€)            | 8,047   | 8,955   | 8,029               |
| MI-free survivors    | 87.74%  | 93.51%  | 91.25%              |
| MACE-free survivors  | 79.72%  | 83.54%  | 76.72%              |
| <b>Diabetics</b>     |   |   |                     |
| N                    | 173   | 162   | 156                 |
| Costs (€)            | 8,792   | 9,034   | 8,317               |
| MI-free survivors    | 87.28%  | 93.83%  | 91.67%              |
| MACE-free survivors  | 73.41%  | 84.57%  | 75.64%              |
|                      | <b>Incremental CE-ratio<br/>adding abciximab (one-<br/>sided 95% upper limit)</b> | <b>Incremental CE-ratio<br/>adding stents (one-sided<br/>95% upper limit)</b> |                     |
| <b>All patients</b>  |   |   |                     |
| MI-free survival     | 12,876 (27,366)   | 39,463 (1,438,868)  |                     |
| MACE-free survival   | 14,198 (49,873)   | 12,228 (30,597)   |                     |
| <b>Non-diabetics</b> |   |   |                     |
| MI-free survival     | 15,713 (36,381)   | 40,936 (ns)   |                     |
| MACE-free survival   | 23,717 (487,232)  | 13,570 (40,555)   |                     |
| <b>Diabetics</b>     |   |   |                     |
| MI-free survival     | 3,695 (42,521)  | 33,219 (ns)   |                     |
| MACE-free survival   | 2,167 (25,246)  | 8,040 (91,103)  |                     |

PTCA=percutaneous transluminal coronary angioplasty; MI=myocardial infarction; MACE=major adverse cardiac event; ns=if efficacy is not significant at 10% then no upper limit for the CE-ratio is calculated.

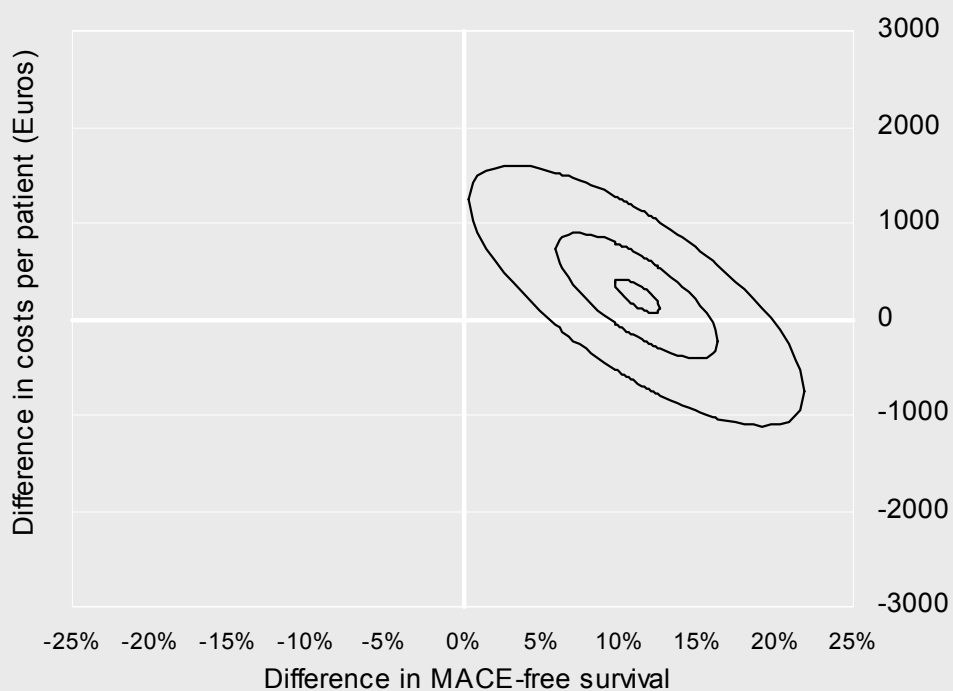
### Cost-efficacy

From the above results, it may be concluded that the combination of abciximab and stenting is not expected to be cost saving within the first 6 months. Table 3 presents the estimates of costs, effects and cost-efficacy ratios for all patients, diabetics and non-diabetics.

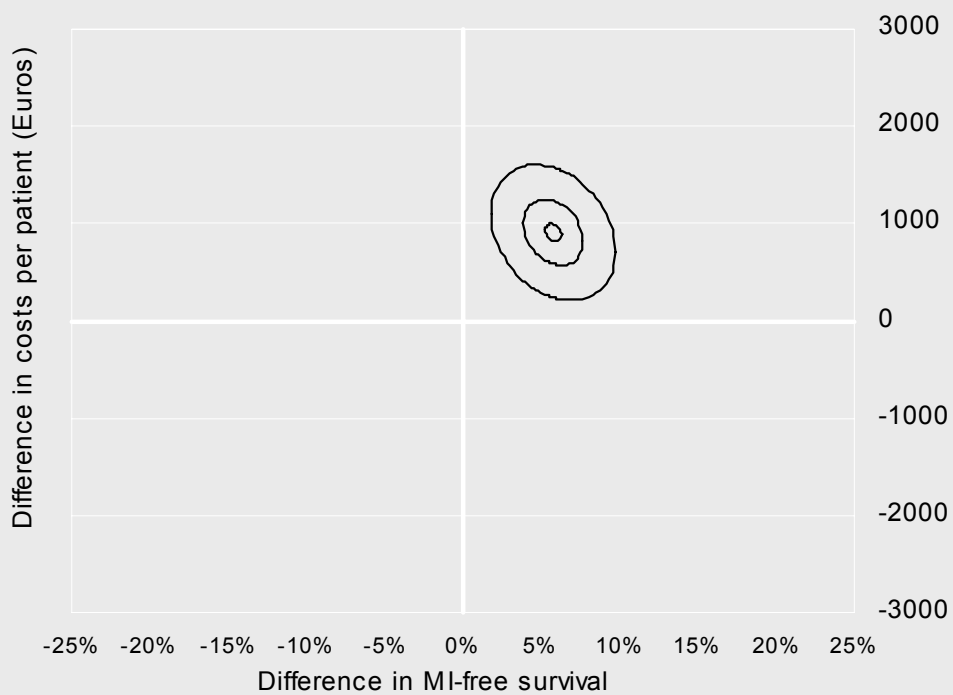
**Figure 1a** The added value of abciximab: diabetics  
MI-free survival after 6 months



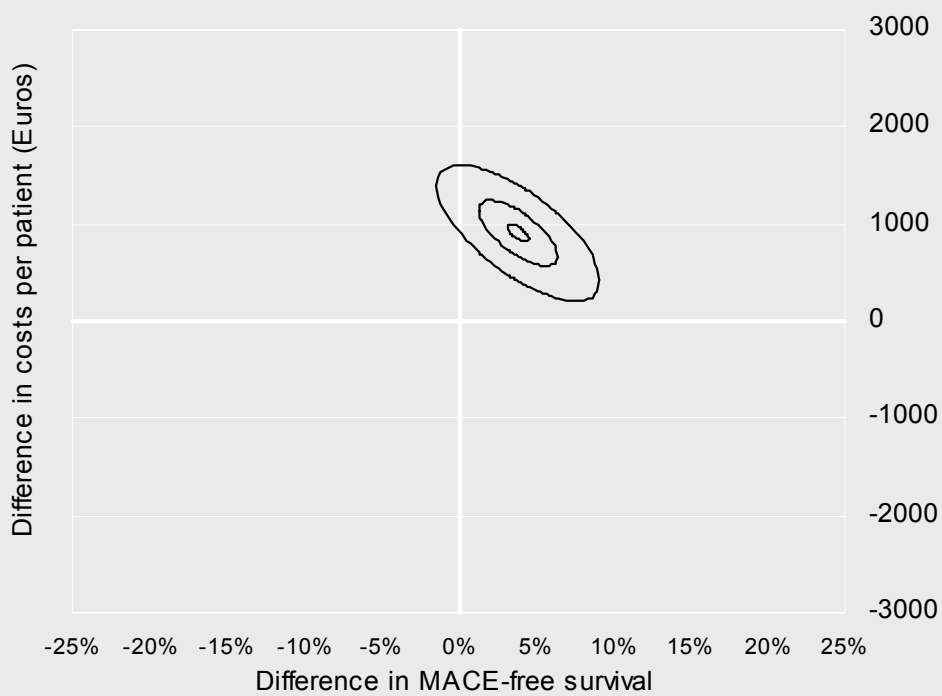
**Figure 1b** The added value of abciximab: diabetics  
MACE-free survival after 6 months



**Figure 1c** The added value of abciximab: non-diabetics  
MI-free survival after 6 months



**Figure 1d** The added value of abciximab: non-diabetics  
MACE-free survival after 6 months



The results show that adding stenting to a procedure where the use of abciximab is planned, may only be considered efficient when the goal is to prevent revascularisations, not so much when the goal is to improve myocardial infarction-free survival. The value of adding abciximab to a stenting procedure differs among subgroups. For the majority of patients, adding abciximab may be efficient especially to increase myocardial infarction-free survival. However, in the subgroup of diabetic patients, adding abciximab affects revascularisations as well, and may be an efficient strategy in terms of myocardial infarction-free survival as well as MACE-free survival.

While there are substantial differences between the point estimates when comparing diabetics and non-diabetics, these differences are not evident when comparing the one-sided 95% upper limits. This is, of course, related to the fact that the subgroup of diabetic patients contained fewer patients. This is confirmed by Figures 1 and 2, which indicate both costs and effects in two-dimensional planes, together with the estimated uncertainties, for diabetic and non-diabetic patients. Figure 1 illustrates the value of adding abciximab to a procedure involving stent implantation, and Figure 2 shows the added value of stenting when the use of abciximab was planned. Points in the right upper quadrant denote that the addition of abciximab (Figure 1), respectively the addition of a stent (Figure 2), is more effective and more costly; the right lower quadrant denotes the addition to be more effective and less costly; the left lower quadrant denotes lower efficacy and lower costs; and the left upper quadrant denotes both higher efficacy and higher costs.

It is noted that there is more uncertainty surrounding diabetic patients, and that there is a substantial probability that the combination of abciximab and stenting might result in cost savings (and more event-free survivors), especially when abciximab is added to a procedure where stenting is scheduled.

## DISCUSSION

The results of the EPISTENT study may help in deciding whether one should add abciximab to an elective stent procedure, or whether one should add a stent to a procedure planned with abciximab. As such, they do not answer the question should one use a stent or abciximab at the first place. For these questions, one should consider the results from the BENESTENT II study (for stenting) [5] or from the EPIC study [18]. In the BENESTENT II study the costs for stenting were estimated at €8,780 per MACE-free survivor [5]. For abciximab the costs per additional myocardial infarction free survivor were estimated in the EPIC study at €2,900 [19]. The result confirm the hypothesis, given that one already has decided to use abciximab, that stenting will further decrease the number of revascularisations in both diabetic and other patients. The costs per additional MACE-free survivor are estimated at €12,000 (95% upper limit (u.l) €31,000); for diabetics at €8,000



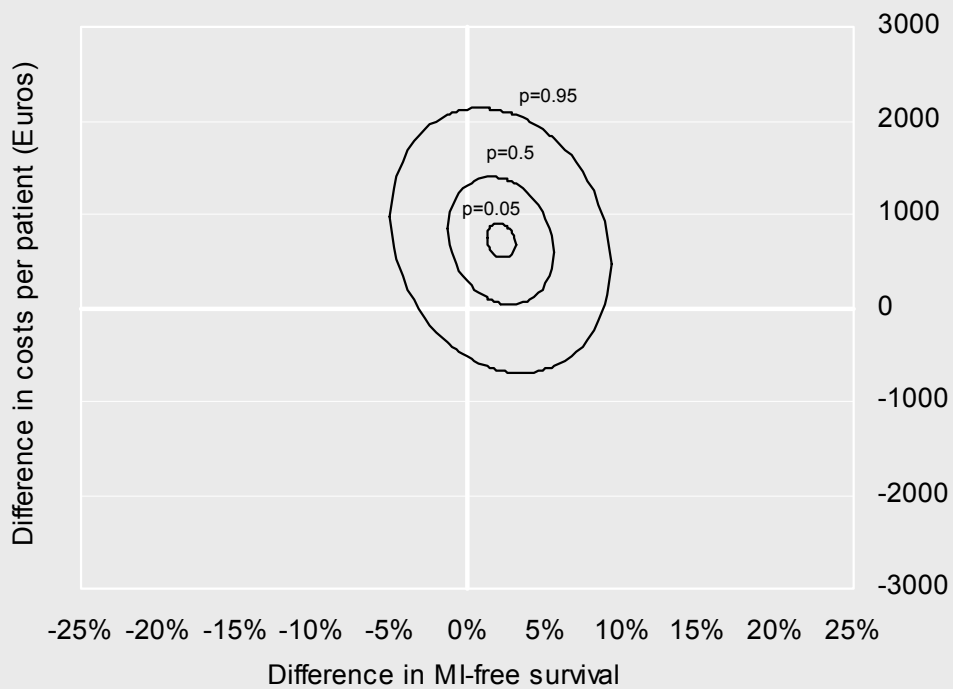
(95% u.l. €91,000). Additionally, the result confirms the hypothesis, given that one will use a stent, that use of abciximab will decrease the incidence of myocardial infarctions. The additional costs per additional myocardial infarction-free survivor are estimated at €13,000 (95% u.l. €27,000); for diabetics at €3,700 (95% u.l. €46,000). Most notably, in the subgroup of diabetic patients, adding abciximab not only improves myocardial infarction-free survival, but also it decreases the revascularisation rate. This results in a cost-efficacy rate of €2,000 per MACE-free survivor (95% u.l. €25,000), and even the possibility of costs savings.

The calculations presented here are obtained by combining event rates in the EPISTENT study with estimated costs from the Dijkzigt hospital in the Netherlands. It is emphasised that the results presented here need to be interpreted with some care since: (1) only direct medical costs have been included, (2) no data on health related quality of life have been included, and (3) no analysis of costs per life year gained has been performed. The trial was not powered to analyse differences in survival, although the 6 month results show a significant difference due to stenting. The recently reported 12 month results confirm this difference, and also show a significant survival difference at that point in time, due to abciximab [20]. These results could be used to calculate an extrapolated survival difference, to estimate future costs and to estimate costs per life year gained. However, we feel that these estimates would need to be surrounded with lots of uncertainties, in light of the limited power and the fact that, until now, stents have never been able to convincingly show a decrease in mortality [21].

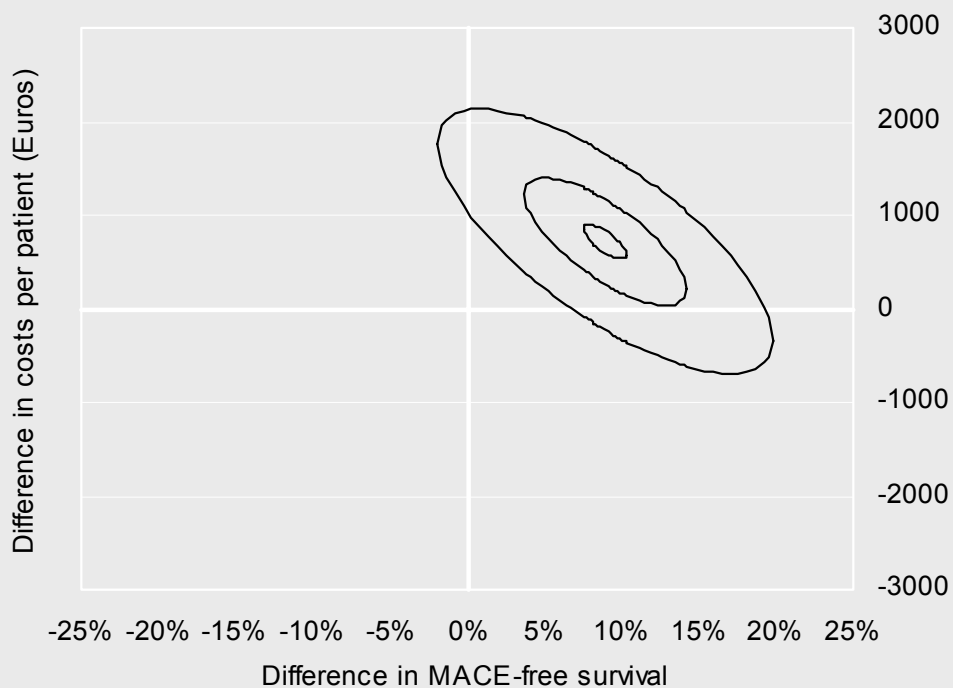
Also, a number of assumptions have been made in the analysis. Most notably, it has been assumed that the results from the EPISTENT trial can be reproduced in The Netherlands. This assumption may not be correct, especially when certain treatment decisions affect the costs and effects. For example, it should be appreciated that the average number of PTCAs per 100,000 citizens is between 115 and 143 in the United States, while it is only about 70 in the Netherlands [22]. Another concern is the definition of efficacy. The analysis includes death, myocardial infarctions and revascularisation procedures in the outcome measure without any distinction with respect to the severity of the various events. This can only be labelled as a very rough approach. When additional research is initiated, it would be worthwhile to incorporate quality of life measures in the assessment of the effects. Additionally, to calculate quality adjusted life years gained, it would be worthwhile to incorporate a utility measure, such as the EuroQol or a patient preference method.

The question can now be raised, how can these results be translated into clinical practice? Clinicians might ask themselves whether these incremental cost-efficacy ratios are acceptable.

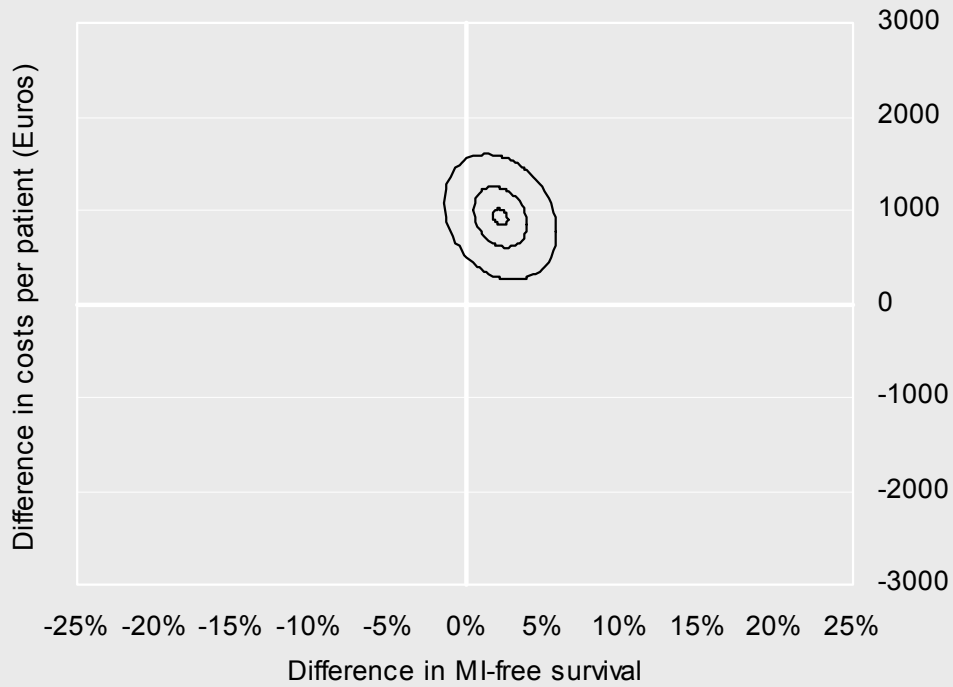
**Figure 2a** The added value of stenting: diabetics  
MI-free survival after 6 months



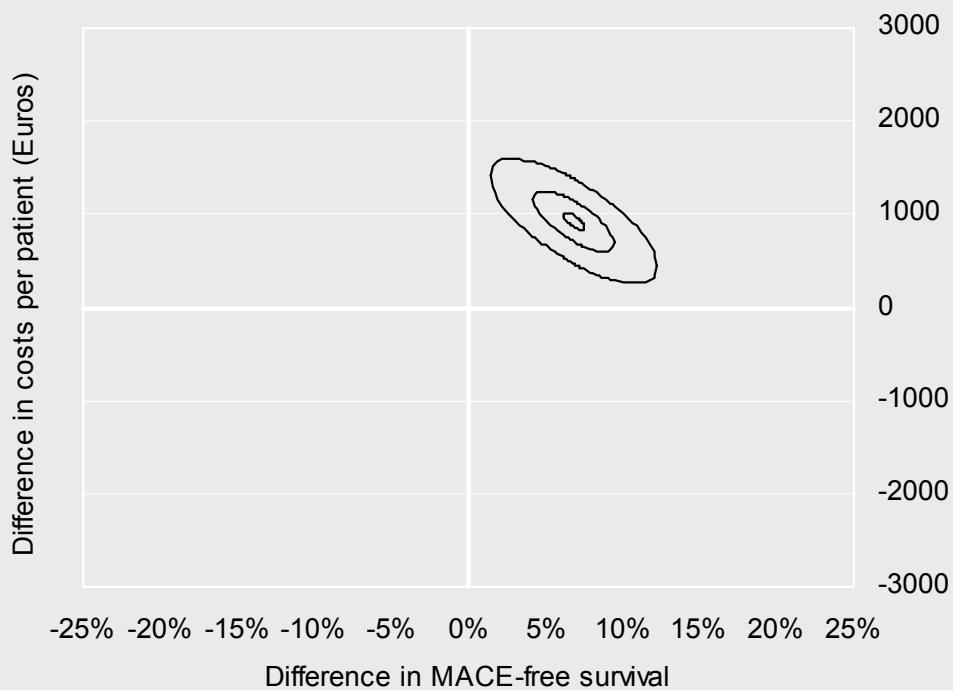
**Figure 2b** The added value of stenting: diabetics  
MACE-free survival after 6 months



**Figure 2c** The added value of stenting: non-diabetics  
MI-free survival after 6 months



**Figure 2d** The added value of stenting: non-diabetics  
MACE-free survival after 6 months



Is it worth €13,000 to prevent a myocardial infarction (in most cases a non-Q wave myocardial infarction), and is it worth €12,000 to prevent a revascularisation? The answers are difficult to give and may also depend on the possibility of finding additional funds. One way may be to limit the combined strategy to diabetic patients for whom the cost-efficacy ratios are much lower, with the need of correspondingly fewer funds. On the one hand, this is due to the fact that fewer patients are treated, on the other hand, to the reduced need for repeat interventions in these patients. However, the latter needs to be interpreted with care. A reduction in the revascularisation rate was demonstrated only in the EPIC trial [9], while in other trials (including the overall results from EPISTENT) this finding could not be replicated. More important than whether this finding is coincidental, may be the question whether one should stent a diabetic patient in the first place. The literature does not present any uniform conclusions about efficacy, let alone about cost-efficacy [23,24]. In such cases, the CE ratio of combined use of stenting and abciximab should be calculated against a plain PTCA procedure or even better, with diabetic patients, against bypass surgery. Indeed, if one buys a Ferrari, it is better to buy one with wheels; however, the question is, of course, whether one should have bought a Ferrari in the first place. As such, a further refinement of whom to stent and who should be given abciximab in the first place, may prompt the creation of an additional budget for treating patients with the combination of the two.

As a conclusion, there are still unanswered questions about which treatment is the most efficient for patients scheduled for revascularisation. Potentially, the main problem may be that a PTCA is already a very efficient procedure and it will always be difficult to improve on something that is already so good. As such, one might conclude that interventional cardiologists are being punished for their own success. However, and this may offer some comfort, there are probably many specialists that would like to be in this position.

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# 5

## **Costs and effects of combining stenting and abciximab (ReoPro<sup>®</sup>) in daily practice**

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## ABSTRACT

*Aim* - The combined use of stents and abciximab in percutaneous coronary intervention has been evaluated in the EPISTENT trial. However, the clinical and economic findings in trials are not necessarily generalisable to a general population setting. We conducted a study in daily clinical practice comparing stented and non-stented patients undergoing coronary angioplasty with abciximab administration. Furthermore, we compare our results with the findings of the EPISTENT trial.

*Methods* - From 1995 to 1999, refractory unstable patients scheduled for angioplasty and receiving abciximab in a Dutch regional hospital were followed prospectively for 6 months. Total costs were considered in addition to 2 composite clinical endpoints: (1) death or myocardial infarction (MI); and (2) death, MI, or any revascularisation procedure (major adverse cardiac events, MACE).

*Results* - Stented patients ( $n=101$ ) experienced less MACE than non-stented patients ( $n=83$ ) (6.9% vs. 16.9%, OR= 0.37,  $p=0.04$ ). The total costs were similar for stented and non-stented patients (€7,844 vs. €7,904,  $p=0.93$ ). Adjustment for baseline characteristics yielded similar results, although significance subsided. The relative risk reduction of 44% that we found closely resembles the 42% that was found in the EPISTENT trial.

*Conclusion* - In everyday practice, as in the EPISTENT trial, the addition of a stent to abciximab treatment does seem to reduce the risk of MACE by about 40% at no additional costs.



## **INTRODUCTION**

A series of randomised controlled trials (RCTs), which directly compared elective stent implantation with balloon angioplasty, have shown that stenting reduces the need for repeat revascularisation procedures [1-7]. However, there is an ongoing debate about the respective merits of RCTs and observational studies in the assessment of treatments [8-12]. The results of RCTs are not necessarily generalisable to a general population setting. For example, it has been shown that patients included in RCTs of cardiovascular drugs have different characteristics from the people who use these products in daily practice [13], and also that the treatment effects of antihypertensive therapy in daily practice may be different from the effects in RCTs [14,15].

Also, the spectrum of patients undergoing a percutaneous coronary intervention in current practice may be much broader than the patients included in clinical trials, since the trials applied strict clinical and anatomical entry criteria. Therefore, it is important to evaluate the effectiveness of stenting under circumstances of everyday clinical practice [11,12]. This has been done already in several observational studies. These studies have found that the widespread use of coronary stents coincided with improved short-term outcomes and reduced or equal revascularisation rates during follow-up [16-18].

Over the recent years GP IIb/IIIa receptor blockers became available, most notably abciximab (ReoPro®). In RCTs abciximab has been shown to be effective in reducing the rate of myocardial infarction (MI) and the necessity for urgent revascularisation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Given the 'separate' positive effects of stenting and abciximab – stents on revascularisation-free and abciximab on MI-free survival – the 'Evaluation of Platelet IIb/IIIa Inhibitor For Stenting Trial (EPISTENT)' study was performed to evaluate whether the combination of abciximab and stenting would lead to a synergistic effect. In this American/Canadian study, the combined use of stents and abciximab indeed turned out to be the superior treatment compared both to abciximab administration alone and to stenting alone [19].

However, again the question remains if this finding applies to everyday clinical practice in Europe as well. In daily practice, does the implantation of a stent have additional value when the patient is already receiving abciximab treatment? As far as we know, this question has not yet been addressed. Here we present a study which included all patients from a regional hospital in the Netherlands (Alkmaar) who were administered abciximab and who were subsequently transported to one of two specialised centers to undergo PTCA either with or without stent implantation. We compare cardiovascular outcome events and costs between stented and non-stented patients. Subsequently, we compare our findings to the EPISTENT study.

**Table 1** Baseline characteristics of non-stented and stented patients in our study <sup>a</sup>

|                                | Non-stented | Stented     | p-value |
|--------------------------------|-------------|-------------|---------|
| Number                         | 83          | 101         |         |
| Age (years)                    | 63.5 ± 2.4  | 62.8 ± 2.2  | 0.67    |
| Male (%)                       | 68.7%       | 80.2%       | 0.09    |
| Braunwald score                |             |             | 0.18    |
| 1b                             | 0.0%        | 3.0%        |         |
| 2b                             | 16.9%       | 25.7%       |         |
| 2c                             | 24.1%       | 24.8%       |         |
| 3b                             | 27.7%       | 26.7%       |         |
| 3c                             | 31.3%       | 19.8%       |         |
| Number of vessels              | 1.58 ± 0.16 | 1.64 ± 0.15 | 0.81    |
| Hypertension                   | 32.5 %      | 27.7 %      | 0.52    |
| Hypercholesterolemia treatment | 60.2 %      | 66.3 %      | 0.44    |
| Diabetes                       | 6.0 %       | 9.9 %       | 0.42    |
| Smoking                        | 30.1 %      | 36.6 %      | 0.43    |
| Family history                 | 43.4 %      | 48.5 %      | 0.55    |
| Previous MI                    | 60.2 %      | 56.4 %      | 0.65    |
| Previous PTCA                  | 14.5 %      | 7.9 %       | 0.23    |
| Restenosis                     | 6.0 %       | 2.0 %       | 0.25    |
| Previous CABG                  | 8.4 %       | 11.9 %      | 0.48    |

<sup>a</sup> MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft

## METHODS

From June 1995 to June 1999, all PTCA patients that received abciximab were followed consecutively for six months. Characteristics such as age, gender, Braunwald score, previous PTCA and other related risk factors were registered at baseline. If the PTCA procedure involved the same vessel that had already been the target of a previous procedure, this is noted as 'restenosis'. Approximately 6 hours after the intervention, creatine kinase and its MB isoenzyme levels in the blood were determined. At 1 month and at 6 months after the procedure the patients revisited the regional hospital for a clinical check-up, including an electrocardiogram (ECG). The following events were recorded: death, myocardial infarction (MI), repeated transluminal coronary intervention, and coronary artery bypass graft (CABG). We used the same criteria as in the CAPTURE and the EPISTENT trial to define a MI [19,20].

**Table 2** Odds ratios for clinical endpoints at 6 months of stented compared to non-stented patients in our study <sup>a</sup>

|                  | Non-stented | Stented | OR unadjusted      | OR adjusted <sup>b</sup> |
|------------------|-------------|---------|--------------------|--------------------------|
| Deaths           | 1.2 %       | 0.0 %   | -                  |                          |
| MIs              | 2.4 %       | 1.0 %   | 0.41 (0.03 – 4.5)  | 0.30 (0.02 – 4.4)        |
| Re-PTCA/re-stent | 9.6 %       | 5.0 %   | 0.49 (0.15 – 1.6)  | 0.73 (0.19 – 2.7)        |
| CABG             | 6.0 %       | 2.0 %   | 0.32 (0.06 – 1.7)  | 0.48 (0.06 – 4.0)        |
| Death or MI      | 3.6 %       | 1.0 %   | 0.27 (0.03 – 2.6)  | 0.20 (0.01 – 2.8)        |
| MACE             | 16.9 %      | 6.9 %   | 0.37 (0.14 – 0.96) | 0.56 (0.19 – 1.7)        |
| Costs (€)        | 7,908       | 7,844   |                    |                          |

<sup>a</sup> MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; MACE, major adverse cardiac event

<sup>b</sup> Adjusted for age, gender, Braunwald score, previous PTCA, restenosis, previous CABG and previous MI.

Two composite endpoints were considered: (1) death or MI; and (2) death, MI, or any revascularisation procedure (major adverse cardiac events, MACE). Costs were calculated by multiplying the number of events recorded in the trial database by the estimates of costs per event. The estimates of these unit costs are derived from The Netherlands and are based on the economic evaluation study from the BENESTENT II trial [3].

Baseline characteristics, outcomes and costs were compared using Fisher's Exact test and the Student's *t*-test. (Adjusted) odds ratios for outcomes were estimated using logistic regression.

## RESULTS

From 1995 to 1999, 184 patients were administered abciximab and then transported for PTCA. Of these patients 83 underwent plain balloon angioplasty and 101 were stented. Baseline characteristics are shown in Table 1. There were no significant differences. However, patients receiving a stent tended to be more often male, hypercholesterolemic, diabetic and smoker. On the other hand, in this group there is also a tendency towards fewer patients with restenosis or a previous MI.

Cardiovascular outcomes for stented and non-stented patients are shown in Table 2. The risk of MACE is significantly lower for stented patients compared to patients who received only balloon angioplasty (6.9% vs. 16.9%, OR=0.37, *p*=0.04). This improved outcome is mainly driven by a decrease in the number of revascularisations.

**Table 3** Costs at 6 months of stented compared to non-stented patients in our study<sup>a</sup>

|                                  | Incidence of events |         | Unit costs (€)             | Costs per patient (€) |         |
|----------------------------------|---------------------|---------|----------------------------|-----------------------|---------|
|                                  | Non-stented         | Stented |                            | Non-stented           | Stented |
| Initial procedure                |                     |         | 2,718 / 3,959 <sup>b</sup> | 2,718                 | 3,959   |
| Abciximab (3 vials)              |                     |         | 1,041                      | 1,041                 | 1,041   |
| Additional stents                | 0                   | 0.20    | 1,354                      | 0                     | 268     |
| Hospital stay (days per patient) |                     |         |                            |                       |         |
| CCU or ICU                       | 0.92                | 0.68    | 969                        | 887                   | 662     |
| Other                            | 5.17                | 3.38    | 469                        | 2,424                 | 1,583   |
| Revascularisation                | 9.64%               | 4.95%   | 3,304 / 3,222 <sup>b</sup> | 318                   | 160     |
| CABG                             | 6.02%               | 1.98%   | 8,622                      | 519                   | 171     |
|                                  |                     |         |                            | 7,908                 | 7,844   |

<sup>a</sup> CCU, coronary care unit; ICU, intensive care unit; CABG, coronary artery bypass graft

<sup>b</sup> Unit costs for non-stented and stented patients respectively

Age, gender, Braunwald score, previous PTCA, restenosis, previous CABG and previous MI were identified as confounders and were subsequently adjusted for. After adjustment the occurrence of MACE after stenting is still decreased compared to plain balloon angioplasty, although not statistically significant (OR=0.56, p=0.28). General risk factors for developing cardiovascular diseases (CVD), such as hypertension, diabetes, smoking, and a history of CVD in the family, were not adjusted for, since their influence was negligible.

Table 3 shows that, although the implantation of a stent increases the cost of the initial procedure with about €1,250 per patient (from €3,959 to €2,718), the total costs after 6 months of follow-up are similar for stented and non-stented patients (€7,844 and €7,904 respectively, p=0.93).

In Table 4 the baseline characteristics of the patients in our study are compared to the patients in the EPISTENT trial. In our study there are less patients with hypertension or diabetes, and more patients who had had a previous MI. Nonetheless, the baseline rate of events without stent implantation is similar in our study as in EPISTENT (death/MI 3.6% respectively 7.8%, p=0.27; MACE 16.9% respectively 20.4%, p=0.56).

**Table 4** Baseline characteristics of patients in our study and of patients in the EPISTENT trial <sup>a</sup>

|               | <b>Our study</b> | <b>EPISTENT</b> | <b>p-value</b> |
|---------------|------------------|-----------------|----------------|
| Number        | 184              | 1,590           |                |
| Age (years)   | 63.2 ± 1.6       | 60 ± 0.5        |                |
| Male          | 75.0 %           | 75.3 %          | 0.93           |
| Hypertension  | 29.9 %           | 51.1 %          | <0.001         |
| Diabetes      | 8.2 %            | 20.0 %          | <0.001         |
| Smoking       | 33.7 %           | 35.7 %          | 0.63           |
| Previous MI   | 58.2 %           | 48.9 %          | 0.02           |
| Previous CABG | 10.3 %           | 8.0 %           | 0.26           |

<sup>a</sup> MI, myocardial infarction; CABG, coronary artery bypass graft

As shown in Table 5, the relative risk reductions (RRR) and the numbers needed to treat to avoid one event (NNT) that we found in our study are similar to the findings in EPISTENT. Looking at death and MIs, 35-43 patients need to be stented to avoid one event; if revascularisations are considered as well, about 13 patients need to be stented to avoid one event.

## DISCUSSION

In our observational study in daily clinical practice, the number of MACE during 6 months of follow-up improved by about 44% after stenting compared to plain balloon angioplasty, whereas the direct medical costs are similar in both groups. Our results correspond very well to the findings in the EPISTENT trial, where a reduction of 42% was found in the incidence of death, MI and target vessel revascularisations. The difference between our study including all revascularisations in the composite endpoint, and EPISTENT including only target vessel revascularisations, is negligible since the vast majority of all revascularisations are indeed target vessel revascularisations [19,21,22]. The fact that the reduction of MACE in our study does not remain significant after adjustment for baseline characteristics is most likely due to the small sample size. The indication as such, that the combined usage of stents and abciximab leads to improved event-free survival in daily practice in Europe, is not a guarantee for widespread use. Many hospitals face budgetary constraints and the use of stents initially is associated with increased costs. However, our study suggests that these additional costs are offset by savings through a reduction in the number of revascularisations and MIs during follow-up.

**Table 5** Relative risk reduction (RRR), 6 months absolute risk (AR<sub>6m</sub>), and 6 month number needed to treat (NNT<sub>6m</sub>) for combined events in our study and in the EPISTENT trial <sup>a</sup>

|           | <b>Our study</b>      |  |                   | <b>EPISTENT <sup>b</sup></b> |  |                                 |
|-----------|-----------------------|--|-------------------|------------------------------|--|---------------------------------|
|           | RRR (%)<br>(95% c.i.) | AR <sub>6m</sub> (%)<br>non-stented<br>/ stented | NNT <sub>6m</sub> | RRR (%)                      | AR <sub>6m</sub> (%)<br>non-stented<br>/ stented | NNT <sub>6m</sub><br>(95% c.i.) |
| Death/ MI | 80<br>(-180-99)       | 3.6 / 0.72                                       | 35 (8-NA)         | 31 (-5-54)                   | 7.8 / 5.5  | 43<br>(24-NA)                   |
| MACE      | 44<br>(-70-81)        | 16.9 / 9.5                                       | 13 (7-NA)         | 42 (24-56)                   | 20.4 / 12.8                                      | 13<br>(9-20)                    |

<sup>a</sup> MI, myocardial infarction; MACE, major adverse cardiac event; c.i., confidence interval; NA, not applicable since OR included one

<sup>b</sup> in EPISTENT only target vessel revascularisations are included in MACE, while we included all revascularisations in our study

An important limitation of our study is that stenting was not randomly assigned, but decided upon by physicians. This may have introduced bias. Despite adjustment for a large number of potential confounding factors, residual confounding due to unmeasured factors cannot be excluded.

In sensitivity analyses of the influence of differences in baseline characteristics on the estimates of the odds ratios, it turned out that previous coronary interventions or MIs have more influence than general risk factors for developing CVD, such as hypertension, smoking and a family history of CVD. Adjustment for diabetes did not influence the OR either. Diabetes is often mentioned as an indicator for inferior outcomes after PTCA [23,24]. In our study group there are fifteen diabetes patients; the percentage of MACE occurring among them did not differ significantly from the non-diabetics (11.8% in non-diabetics vs. 6.7% for diabetics,  $p=1.0$ ).

The issue of the additional value, in actual clinical practice, of stent implantation in PTCA patients who are already administered abciximab, remains an important topic to be addressed. In a relatively small study we found a beneficial effect of stenting, which is very comparable to the findings in the EPISTENT trial. In everyday practice, the addition of a stent to abciximab treatment does seem to yield additional benefit. However, this finding needs to be confirmed in larger scale studies.

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# 6

## **Variability in abciximab (ReoPro®) prescribing: evidence based or budget driven?**

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## ABSTRACT

*Aim* - Abciximab improves outcomes in patients undergoing percutaneous transluminal coronary intervention (PTCA). Clinicians, however, have expressed concerns that they do not have enough budget to administer abciximab to all eligible patients. We studied the patterns of prescribing of abciximab and identified factors that correlate with the level of usage.

*Methods* - In each of all 13 Dutch PTCA centers one opinion-leading cardiologist was approached to provide data on the abciximab prescribing in their center and to co-operate in an interview on this topic. We performed linear regression analysis in which the level of abciximab prescribing was the dependent variable. Potential determinants investigated were the number of PTCAs performed, the criteria for abciximab prescribing, funding and possible financial restrictions, participation in clinical trials in the past, percentage stenting, and desired level of abciximab prescribing.

*Results* - All 13 PTCA centers in the Netherlands participated in our study. The level of abciximab prescribing varied from 2% to 36% of all PTCAs. The criteria for patient selection significantly differed between centers. Together: budget, investigatorship, size, and type of the institution were highly predictive for the level of abciximab prescribing ( $R^2=0.93$ ,  $p<0.001$ ). The more patients doctors had included in clinical trials in the past, the higher was the likelihood that they prescribed abciximab.

*Conclusion* - Shortly after its introduction, patterns of abciximab prescribing varied widely between PTCA centers. There was no agreement on which patients to select for this preventive treatment. Budget and involvement in clinical trials in the past were important predictors of the level of prescribing in each center.

## **INTRODUCTION**

Today's health care increasingly has to face budget constraints, while the possibilities for treatment are getting more and more advanced and expensive [1]. In particular biotechnology has increased our understanding of disease processes and has facilitated the discovery and production of therapeutic proteins. Several biotechnology drugs have entered the market, and many others are expected to follow [2,3]. On the one hand this implies a promise for the future, on the other hand it raises concerns about the increasing costs of health care, since most innovative drugs bear considerable price tags. The risk of waste on expensive and less effective drugs has so be set against the risk of strangling innovations and inducing suboptimal quality of care. Finding a balance in this delicate equilibrium is one of the biggest challenges in medical decision making. Case studies of existing drugs can be an important means to improve our decision-making in the future. Therefore, we present here the case of abciximab (ReoPro®), a new drug that inhibits platelet aggregation and is used in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). PTCA is a technique to dilate narrowed parts of the coronary artery in patients with angina pectoris or myocardial infarction by inserting a small balloon in the coronary artery and inflating it at the spot of the stenosis. The two main complications associated with a PTCA procedure are abrupt vessel closure (4-9% of patients), leading to myocardial infarction or death, and gradual re-occlusion of the coronary artery (restenosis, 20-55% of patients). Based on the first trial with high-risk PTCA patients, in 1994 the European Medicines Evaluation Agency (EMEA) approved abciximab as an adjuvant treatment to prevent ischaemic cardiac complications in high-risk patients undergoing PTCA [4,5]. Subsequent trials demonstrated that abciximab also improved outcomes in a broader category of patients [6-8] and the official indication was extended to include all PTCA patients by the end of 1997. From a cost-effectiveness perspective, however, it may be worthwhile to know in which category of patients the benefit of abciximab is largest. Data on cost-effectiveness and on specific subsets of patients has so far been limited and inconclusive [9-13]. In 1998 in the Dutch media cardiologists have expressed their concern that their budgets do not allow them to give abciximab to all eligible patients. Public exposure of this issue has been high. We studied the patterns of prescribing of abciximab and identified factors that determine the level of prescribing per center.

## **BACKGROUND**

In the Dutch health care system all hospitals are budgeted. The budget for pharmaceuticals is the responsibility of either the department of Hospital Pharmacy, or of each clinical department separately for their own share in it. The procedure cost of a PTCA procedure (fixed costs plus variable costs, without hospital days) amounts

to about €2,700 without stent implantation, and €4,100 with the implantation of one or more stents [14]. The prescribing of abciximab adds about €1,200 to this amount. A stent is a tiny wire mesh tube, which is implanted in the dilated artery to prevent acute coronary occlusion and later restenosis. It has been estimated that 60-80% of all PTCA procedures involve the implantation of a stent [15].

Economic evaluations from a societal perspective have demonstrated that the additional costs of abciximab are partly offset by savings through a reduction in the number of revascularisations and MIs during follow-up [12,16,17]. From the perspective of the hospital management, however, these savings may not actually become apparent, since within the hospital the total number of MIs treated or the number of revascularisations performed will probably not decrease for various reasons (e.g. existing waiting lists). In the Netherlands, there are no official national guidelines in use concerning the prescription of abciximab.

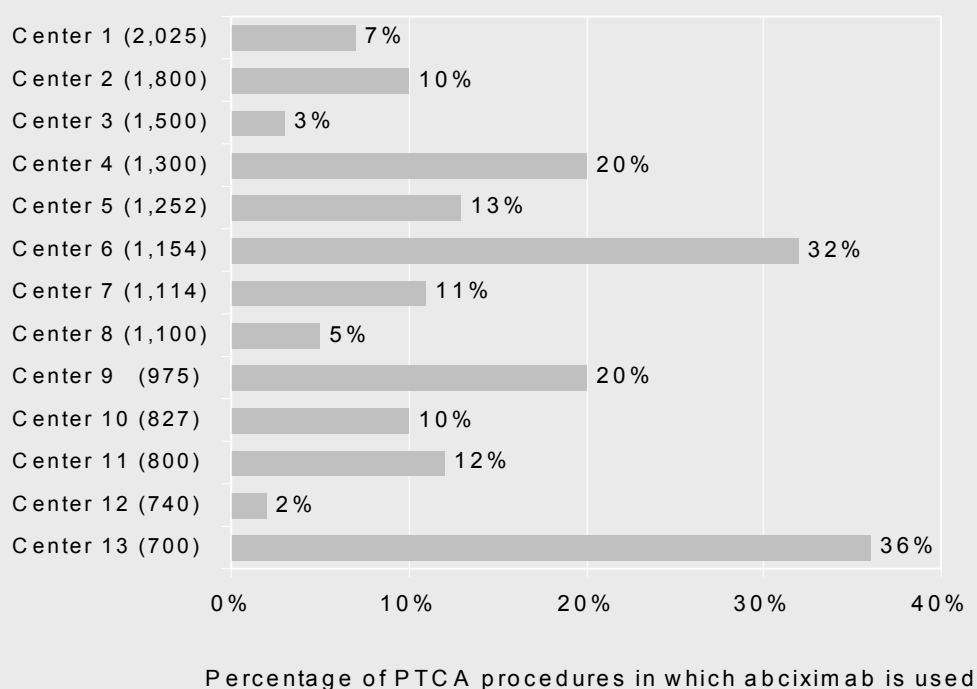
### **METHODS**

From April till August 1999 one opinion-leading cardiologist in each of all 13 PTCA centers in the Netherlands was approached to provide data on the abciximab prescribing in his center and to co-operate in an interview on this topic. Names of the opinion-leading cardiologist in each center were given to us by a leading Dutch cardiologist. All cardiologists were first sent a letter, in which they were requested to look up the data that were asked for in the questionnaire that was included. Subsequently we contacted them again to collect the filled-in questionnaires and discuss the outcomes. Ten respondents were interviewed in person, 3 respondents were interviewed by telephone, and 1 respondent returned the questionnaire by fax. All respondents provided us with exact data on the budget arrangements and the utilisation of abciximab in 1998.

The primary outcome measured was the level of abciximab prescribing in 1998, which was deduced from the number of PTCAs performed and the number of patients treated with abciximab. Potential determinants which were addressed in the questionnaire concerned criteria for prescribing, the funding and possible financial restrictions on the treatment, participation in clinical trials in the past, the proportion of patients receiving stents, and opinion on the appropriate level of abciximab prescribing. A summary of the interview and the provided data was sent to each respondent for confirmation. The quantitative data provided were analysed using both univariate and multivariate linear regression analysis, with the level of abciximab prescribing being the dependent variable.

The level of abciximab prescribing is expressed as the percentage of all PTCA procedures in which abciximab was used. 'Budget' refers to any imposed financial restrictions and is expressed as the percentage of PTCAs in which abciximab treatment was allowed.

**Figure 1** Levels of abciximab prescribing in the 13 PTCA centers in the Netherlands



*(between parentheses are the number of PTCAs that are performed in each center)*

‘Investigatorship’ is defined as the number of patients that was included in clinical trials with abciximab in the past (in the center in which the respondent was working at that time). ‘Type of institution’ refers to academic and non-academic hospitals. ‘Size of institution’ is the number of authorised beds in the total institution, including departments other than Cardiology.

## RESULTS

The level of overall abciximab prescribing varied considerably between centers, ranging from prescription in 2% to 36% of all PTCAs performed (see Table 1 and Figure1). Of total abciximab prescribing 75% was administered surrounding stenting procedures.

Nine out of the 13 centers indicated that the use of abciximab was restricted because of economic reasons. Only 4 centers were completely satisfied with the available budget at that time (their prescribing ranged from 13% to 36%). Two of these had no budgetary constraints at all, and the other 2 reported that the available budget was sufficient.

**Table 1** PTCA, abciximab, budget and stenting in all 13 Dutch PTCA centers in 1998

|  | <b>minimum</b> | <b>maximum</b> | <b>median</b> | <b>average</b> |
|--|----------------|----------------|---------------|----------------|
| Number PTCA's performed                                    | 700            | 2,025          | 1,114         | 1,176          |
| Number of abciximab treatments                             | 15             | 364            | 145           | 153            |
| % of PTCA's in which abciximab is used                     | 2%             | 36%            | 11%           | 14%            |
| Desired reasonable percentage of prescribing               | 13%            | 95%            | 28%           | 34%            |
| Percentage of abciximab used electively                    | 0%             | 90%            | 35%           | 37%            |
| Percentage of abciximab used with stents                   | 33%            | 96%            | 76%           | 75%            |
| Budget   |                |                |               |                |
| - number of abciximab treatments                           | 0              | 460            | 84            | 128            |
| - % of PTCA's in which abciximab can be used               | 0%             | 40%            | 10%           | 12%            |
| Number of patients included in clinical trials in the past | 0              | 184            | 15            | 37             |
| % of PTCA's in which a stent is implanted                  | 40%            | 85%            | 60%           | 61%            |

*PTCA, percutaneous transluminal coronary angioplasty*

Criteria for the selection of patients eligible for abciximab treatment varied between centers. In total, half of all treated patients received abciximab not before PTCA to prevent thrombotic complications (elective use), but during or after the procedure to treat impending complications or to improve suboptimal results (rescue or bail-out use). Five centers used abciximab almost exclusively (90-100%) as a rescue drug. These 5 centers all indicated that they used this strategy out of budgetary considerations, to limit the administration of scarce abciximab to those patients who were most likely to benefit. Other centers administered at least part of their abciximab electively. The various criteria for prescribing are summarised in Table 2. When respondents were asked how much abciximab would reasonably be needed and which would be the appropriate criteria for prescribing, the answers also were very different from one center to another (see 'Desired reasonable percentage of prescribing' in Table 1).

As is shown in Table 3, the use of abciximab was higher in academic centers than in non-academic hospitals (not statistically significant). In all academic centers except one, abciximab was financed from the Cardiology budget, while in all non-academic centers abciximab was part of the budget of Hospital Pharmacy.

| <b>Criterion</b>                         | <b>Number of centers using this criterion</b> | <b>(% of all 13 centers)</b> |
|--|---|------------------------------|
| Rescue or bail-out situations            | 13  | (100%)                       |
| Elective prescribing                     |   |                              |
| PTCA of a bypass graft                   | 7   | (54%)                        |
| Angiographic suspicion of a thrombus     | 5   | (38%)                        |
| Myocardial infarction patients           | 4   | (31%)                        |
| Unstable patients                        | 3   | (23%)                        |
| Multi-vessel disease                     | 2   | (15%)                        |
| Complex or extensive lesions             | 2   | (15%)                        |
| Diabetic patients with very bad arteries | 1   | (8%)                         |

*PTCA, percutaneous transluminal coronary angioplasty*

In univariate regression analysis, budget and investigatorship (the number of patients included in clinical trials with abciximab in the past) were the most important determinants to explain the variation in the current level of abciximab prescribing in each center (Table 4). The higher the budget and the higher investigatorship, the higher the level of use.

Using a multiple linear regression model, we found that together four parameters were highly predictive of the level of prescribing ( $R^2=0.93$ ,  $p<0.001$ ) namely: budget, investigatorship, type of institution and size of institution (Table 5).

## DISCUSSION

We found a large variability in the level of abciximab prescribing, which could be largely explained by budget, investigatorship, and type of institution (academic/non-academic). In the literature, investigatorship has already been identified as an important determinant for drug prescribing before. Pieters described the ‘marketing push’ of clinical trials for the case of interferon [18]. Clinical trialists are likely to have earlier and better knowledge and prepare budget decisions in a more timely fashion, which may result in more early use of the product. On average more abciximab was used in academic than in non-academic hospitals, although this difference was not statistically significant due to the small number of PTCA centers in the Netherlands ( $n=13$ ). Since academic centers are more research oriented, they are probably faster to pick up new developments. The fact that abciximab is financed from the budget of Hospital Pharmacy in most non-academic centers and financed through the department of Cardiology in most academic centers, may also partly explain the difference between academic and non-academic centers.

|   | <b>Academic</b>                                | <b>Non-academic</b>                    | <b>p</b> |
|---|--|--|----------|
| Budget (percentage)   | 15.0%  | 6.3%                                   | 0.27     |
| Actual percentage of PTCAs in which abciximab is prescribed | 16.3%  | 10.2%                                  | 0.33     |
|   | <b>Dept. Cardiology responsible for budget</b> | <b>Pharmacy responsible for budget</b> | <b>p</b> |
| Budget (percentage)   | 15.4%  | 5.5%                                   | 0.21     |
| Actual percentage of PTCAs in which abciximab is prescribed | 16.0%  | 10.6%                                  | 0.39     |

*PTCA, percutaneous transluminal coronary angioplasty*

The situation that we encountered, in which non-medical factors like budget and investigatorship so strongly determined the level of abciximab prescribing, could only exist because there was no agreement on the appropriate criteria for abciximab prescribing. We found that there are large differences in the criteria to select patients for abciximab administration. Rescue use of abciximab is frequently practised although this strategy has hardly ever been tested in clinical trials and is not an approved indication. This indicates that there is budgetary pressure but also, more importantly, that there is a problem to choose beforehand which patients to prescribe abciximab. This is a common problem in preventive therapies. It has been stated that no PTCA patient subgroup has been identified who do *not* benefit from treatment with abciximab [19,20]. One could compare this with cholesterol lowering treatment with statins, which has been proven effective in a broad category of patients, including people with just average cholesterol levels [21-23]. The question then becomes a cost-effectiveness issue: in which subgroups of patients we feel the balance between effects and costs is still acceptable, and in which not? On statin prescribing consensus has been reasonably established by now [24], but for abciximab treatment the debate still has to begin. Moreover, for abciximab patient numbers are much smaller and evidence on subgroups and cost-effectiveness is much more limited than for statins. There are already some indications that abciximab may be especially beneficial in patients with evolving myocardial infarction, unstable angina or diabetes [10,19,20,25]. More research and debate in the area of cost-effectiveness in specific subgroups is needed.

In 1998, 75% of total abciximab prescribing took place surrounding stenting procedures, although this indication had not been separately established.



**Table 4** Determinants of the level of abciximab prescribing in 1998: univariate linear regression analysis

|  | coefficient | p       | R <sup>2</sup> |
|--|-------------|---------|----------------|
| Budget (percentage)  | 0.82        | < 0.001 | 0.77           |
| Number of patients included in clinical trials in the past | 0.001       | < 0.001 | 0.66           |
| Percentage of PTCAs in which a stent is implanted          | 0.58        | 0.007   | 0.45           |
| Size of institution (number of beds)                       | 0.0002      | 0.05    | 0.25           |
| Desired reasonable percentage of prescribing               | 0.21        | 0.12    | 0.13           |
| Percentage of abciximab prescribed electively              | 0.13        | 0.14    | 0.11           |
| Number of PTCAs performed                                  | - 0.0001    | 0.32    | 0.06           |
| Budget responsibility (Pharmacy / Dept. Cardiology)        | - 0.05      | 0.39    | 0.00           |
| Type of institution (academic / non-academic)              | 0.14        | 0.33    | 0.00           |

*PTCA, percutaneous transluminal coronary angioplasty*

The clinical trials performed with abciximab so far had focussed primarily on balloon patients; however, some patients underwent bail-out stenting as well [26,27]. Only in 1999 the indication of abciximab was officially extended to include its prescribing with stents as well, based on a fourth randomised controlled trial investigating the effects of combining both stenting and abciximab [8]. Apparently, the official broadening of indications lags behind the practice in real life.

In this study we did not investigate patient records, but we used data that the opinion-leading cardiologists from each center reported to us. All PTCA centers in The Netherlands participated in our study (not a sample). The use of abciximab is such an innovative and expensive therapy, that the policy on, and the budget for its administration, is agreed upon within the team of cardiologists, and does not vary from person to person within a center. As such, we feel that the data that we obtained are valid and representative. In addition, any potential lack of precision has certainly not hampered the interpretation of the data. The differences between centers are so large, that very clear associations could be established, as can be seen in the results from the linear regression analysis ( $R^2=0.96$ ,  $p=0.0003$ ). In theory, differences in patient characteristics may be an important determinant to explain the observed variation in abciximab prescribing, which we did not investigate. However, each center included in our study was designated by the government to provide highly specialised interventional cardiology care to all patients in their catchment area. Together, these 13 centers serve the whole of the Netherlands. Therefore, we think that it is highly unlikely that were considerable differences in patient mix between centers.

The variability in prescribing may be partly due to the fact that abciximab had only recently been approved for a broad category of patients.

**Table 5** Determinants of the level of abciximab prescribing in 1998: backwards multivariate linear regression analysis

|  | value   | p     |
|--|---------|-------|
| (Intercept)  | 0.0830  | 0.059 |
| Budget (percentage)  | 0.5582  | 0.016 |
| Number of patients included in clinical trials in the past | 0.0010  | 0.005 |
| Type of institution (academic / non-academic)              | 0.0702  | 0.046 |
| Size of institution (number of beds)                       | -0.0001 | 0.086 |

$R^2=0.93$ ,  $p<0.001$

In theories of diffusion of innovations, it is well known that in an early phase only a small group of enthusiasts uses the product, the early adopters [28]. In the transition phase from prescribing by early adopters to prescribing by the majority, large differences in level of prescribing can appear. This was seen as well in the early phases of stent prescribing [29]. Therefore, it would be interesting to see what the pattern of prescribing of abciximab and other GP IIb-IIIa blockers looks like in a few years. It takes time before new knowledge is generally diffused into medical practice [30]. Our study presents just a snapshot of a field with rapid developments. In 1998 abciximab was the only available representative of a new category of drugs. By now, two drugs with the same mechanism of action have already entered the market: eptifibatide and tirofiban [31-35].

## CONCLUSION

In conclusion, in 1998 patterns of abciximab prescribing varied significantly between PTCA centers. Since there was no agreement on the appropriate indications to select patients eligible for treatment, other factors such as budget and investigatorship had a large influence on the level of prescribing. The cost-effectiveness issue of whom to treat and whom not needs to be made explicit and ultimately needs to be agreed upon by cardiologists and budget keepers on a national level. More innovative biotechnology drugs are about to enter the market in the coming years. This example has illustrated the uncertainties and practice variation that can be associated with that. Government and health care professionals should be aware of that and try to prevent the resulting retreat from evidence based medicine into budget based medicine.

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# 7

## **The diffusion of recombinant Factor VIII: a study of patients' preference**

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## **ABSTRACT**

*Aim and methods* - In comparison with other biotech substitutions, the adoption of recombinant Factor VIII (rFVIII) has been relatively slow. We sent a postal questionnaire to all Dutch hemophilia patients, to determine which factors predict whether a patient uses plasma derived FVIII (pdFVIII) or rFVIII and to investigate patients' opinions about both products.

*Results* - Older age, infection with HIV or hepatitis C, and having family members who use pdFVIII, were negatively associated with switching from pdFVIII to rFVIII. Innovativeness, having family members who use rFVIII, and treatment in a large hemophilia treatment center, were positively associated with switching. Generally the respondents did not see large differences between rFVIII and pdFVIII, except for the risk of infections and the knowledge on long-term effects (both larger for pdFVIII).

*Conclusion* - Although hemophilia patients may well represent one of the most empowered patient groups, physicians appear to have been very influential in choosing between pdFVIII and rFVIII.

## **INTRODUCTION**

Starting in 1982 with the introduction of recombinant human insulin, over 50 biopharmaceuticals have been introduced to the market in the last two decades [1,2]. Attitudes towards modern biotechnology and life sciences are ambivalent. On the one hand, these developments are considered as a major force for medical progress and innovation. On the other hand there is concern about the health, environmental and social hazards of advanced technologies. People are aware that scientific developments may have negative effects as well. This is true especially for hemophilia patients.

The discovery in 1964, that Factor VIII is concentrated in cryoprecipitate, was an enormous step forward in the treatment of hemophilia, which until then could only deploy infusion of whole plasma. Further purification led to what is generally called plasma derived Factor VIII (pdFVIII). The enthusiasm that greeted these advances, however, was soon dimmed by the discovery that many products were contaminated with viruses. In the Netherlands, 16-17% of the hemophilia patients who were treated with clotting factor products before 1985 became infected with the human immunodeficiency virus (HIV) [3,4]. In addition, the large majority (about 80%) of patients have been infected with hepatitis C virus [5,6]. Since the early 1980s methods such as donor screening, heat treatment, solvent detergent treatment and immunoaffinity purification, have been developed to inactivate infectious agents. Infections with HIV have not been documented after 1985 in the Netherlands, and Factor VIII (FVIII) concentrates have been free from hepatitis C virus since 1991 [5]. Because of this history of infectivity with plasma derived clotting factors, one may have expected that recombinant Factor VIII (rFVIII), which was introduced in the Netherlands in 1995, would receive a warm welcome and would be quickly adopted by the market. This, however, has not been the case. While recombinant human insulin and recombinant human growth hormone have quickly replaced their non-biotech counterparts, and while the recombinant follitropins have captured 80% market share 4 years after their introduction, rFVIII is still only used by about 50% of patients in the Netherlands [7-10].

Apparently, doctors or patients are hesitant to adopt rFVIII. Reasons for that could be several. They may fear some long-term unforeseen negative effect caused by the use of rFVIII. They may be afraid of increased antigenicity of rFVIII, as this was debated in the early 1990s [11,12,13], even though the current scientific belief is that this is not the case [14-16]. Loyalty towards the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB), the major provider of pdFVIII in the Netherlands, might be another reason. Since in the past the prevalence of HIV positivity was highest in countries that predominantly used FVIII preparations derived from plasma of paid donors from the United States [4], there might be a preference for a Dutch not-for-profit organisation with non-paid donors.

Also, it has been argued that it is not possible to switch all patients to rFVIII, even if they would want so, because the supply of rFVIII is not sufficient [10]. Indeed, at the time of our study there was a sudden shortage of rFVIII, as Bayer, one of the major producers of rFVIII, had just suspended market release for its worldwide market. [17] In addition, there may be doubts about the advertised increased safety of rFVIII with regard to transmission of infections. The first rFVIII preparations contained plasma derived albumin as a stabiliser. In 1999 and 2000, three virtually albumin-free formulations (Refacto<sup>®</sup>, Kogenate Bayer<sup>®</sup> and Helixate NexGen<sup>®</sup>) were introduced. They contain 1000 times less plasma derived albumin than the former formulations, and have an additional detergent based purification step, further reducing the potential for virus transmission [18].

As far as we know, the factors that underlie the choice for either plasma derived or rFVIII have never been systematically studied. Who is the most influential in choosing between pdFVIII and rFVIII: the doctor or the patient? Can the adoption of rFVIII be predicted from medical characteristics such as severity of the disease, treatment modality, or infections contracted through the use of clotting factors (HIV, hepatitis C)? What do patients actually think on the safety and antigenicity of rFVIII and pdFVIII? To address these questions we sent a postal questionnaire to all hemophilia patients in the Netherlands. The objective was to investigate the opinions of hemophilia A patients on the choice between pdFVIII and rFVIII, and to determine which factors predict whether a patient uses pdFVIII or rFVIII.

## **METHODS**

### ***Mailing procedure***

The study was carried out as part of the Hemophilia in the Netherlands 5 (HiN-5) project. During the past 30 years, the effects of changes in hemophilia treatment have been monitored by four nation-wide postal surveys among Dutch hemophilia patients conducted in 1972, 1978, 1985 and 1992. In April 2001, patients received a letter about the forthcoming HiN-5 study on hemophilia. Where possible, this announcement was sent by their physician. Other patients were first informed by the Dutch Hemophilia Patients Society or directly by the Study Group HiN-5. All hemophilia patients who were listed with the hemophilia treatment centers, with the Dutch Hemophilia Patients Society, or on updated mailing lists from previous survey(s) were included in the mailing. After an extensive search for addresses the questionnaire was sent to 1,566 patients in May 2001. The closing date for data collection for the current study was set at 12 September 2001.



## **Content**

The prestructured questionnaire in 2001 was largely based on the four previous questionnaires. For this study we added specific questions which followed from a prior model which we developed that incorporated all factors we assumed to be predictive of the choice between recombinant and plasma derived clotting factors. To formulate this model and these questions, literature on clotting factors was consulted, and interviews were held with patients and representatives of the Dutch Hemophilia Patients Society, hemophilia treating physicians, and clotting factor producers. Before the questionnaire was actually sent out, a small number of patients and a panel of experts was asked to complete the questionnaire and to give their comments. These 'pilots' were helpful in optimising the structure and content of the questionnaire.

Questions on age, type of hemophilia, severity of disease, treatment modality, inhibitor formation, infectious diseases (HIV, hepatitis C), treatment center, membership of the Dutch Hemophilia Patients Society, education level and net income were routinely included in the questionnaire. Items were added on: attitude towards innovations (innovativeness), aversion against switching, empowerment, first clotting factor used, current product used, consideration of future product switch, clotting factor used by family members, number of family members with HIV or hepatitis C through the use of clotting factors, most important influence in clotting factor choice (respondent himself, physician, or both equally influential), physician's advice (recombinant, plasma derived or neutral), preference for a specific producer (Dutch over foreign, not-for-profit over for-profit), and opinion on albumin-free formulations of rFVIII (5-points scale: large deterioration, deterioration, no difference, large improvement, improvement). The first three items are described in Table 1, and were included at the beginning of the questionnaire, before the issue of recombinant versus plasma derived clotting factors was introduced.

From a list of 8 characteristics which may be important to patients in choosing between different clotting factor products (price, effectiveness, user friendliness, producer's image, knowledge on long-term effects, risk of infections, risk of product shortages and risk of inhibitor formation), respondents were asked to rank the five most important characteristics (5 through 1 points). The average rating for a product characteristic could be 5 at the most (if all respondents ranked the characteristic as the most important one), and 0 at the least (if none of the respondents selected the characteristic in the top 5 most important). In addition, their opinion on the 8 characteristics was asked on a 5-points scale (-2 very favourable for plasma, -1 favourable for plasma, 0 the same for plasma and recombinant, 1 favourable for recombinant, 2 very favourable for recombinant).

**Table 1** Selection of items included in the questionnaire

**Innovativeness**

- If a new treatment for hemophilia would become available, e.g. gene therapy, how would you react to that?
  - 1 very negative
  - 2 negative
  - 3 neutral
  - 4 positive
  - 5 very positive
- In general, if a new treatment for hemophilia would become available, when would you adopt it?
  - 1 never
  - 2 when the treatment can hardly be escaped anymore
  - 3 when the treatment is proven superior in a large number of patients,
  - 4 when the treatment succesful in some other patients
  - 5 immediately
- With regard to the adoption of the latest insights and treatments in health care, patients can be categorised into five groups. In which group would you place yourself?
  - 1 laggards (10%)
  - 2 late majority (35%)
  - 3 early majority (35%)
  - 4 early adopters (15%)
  - 5 innovators (5%)

**Empowerment**

- I always make clear to my physician which treatment I prefer myself.
- I am well informed about the different treatment possibilities for hemophilia.
- I follow my physician's advice without questioning.\*
- Besides the information my physician gives me, I look for information about clotting factors myself, as well.
- When my physician proposes a certain treatment, I ask if there are other treatment options as well.
  - 1 not at all
  - 2 a little bit
  - 3 quite a lot
  - 4 very much

**Aversion against switching**

- Switching from one clotting factor product to another may cause problems (e.g. inhibitor formation).
- If you are doing well with your current treatment, you should never change to another clotting factor product.
  - 1 totally disagree
  - 2 disagree
  - 3 neither agree nor disagree
  - 4 agree
  - 5 totally agree

\* reverse coding

## **Analysis**

As we were interested in the choice between, and the opinions about rFVIII and pdFVIII, we included in the analysis only patients with hemophilia A who had used FVIII during the 1½ year preceding our questionnaire, and for whom we knew whether the first clotting factor product used had been recombinant or plasma derived. The type of first clotting factor used (recombinant or plasma derived) was investigated in relation to year of birth. In this analysis year of birth was used as a marker for the year of first treatment.

Subsequently, to study switching behaviour, we included only those respondents who had started on plasma derived clotting factor, and excluded the respondents who had started on rFVIII, as switching from rFVIII to pdFVIII is very rare. Odds ratios (OR) for the association with switching from pdFVIII to rFVIII were calculated by use of the logistic regression technique for all factors in our prior model. The factors that were statistically significantly associated with switching in these univariate analyses were subsequently included in a multivariate logistic regression model to calculate the adjusted ORs. The severity of hemophilia was classified according to the residual percentage of FVIII clotting activity: severe (<1%, i.e. <1IU/dl), moderate (1-5%), or mild (>5-40%).

Hemophilia treatment centers were categorised into 'small' and 'large' centers according to the number of respondents ( $n \leq 10$  respondents, respectively  $n > 10$ ). Different items that were designed to measure one common factor, such as e.g. the three items on innovativeness, were clustered together (as the average over the items), if Cronbach's alpha for correlation was  $\geq 0.70$ .

For each respondent, the opinion on each of the eight product characteristic was multiplied with the importance attached to that characteristic. The sum of these eight multiplications was used as a summarising measure of the respondent's opinion on recombinant versus plasma derived clotting factor (range -30 to 30).

## **RESULTS**

### ***Response, participants and first use***

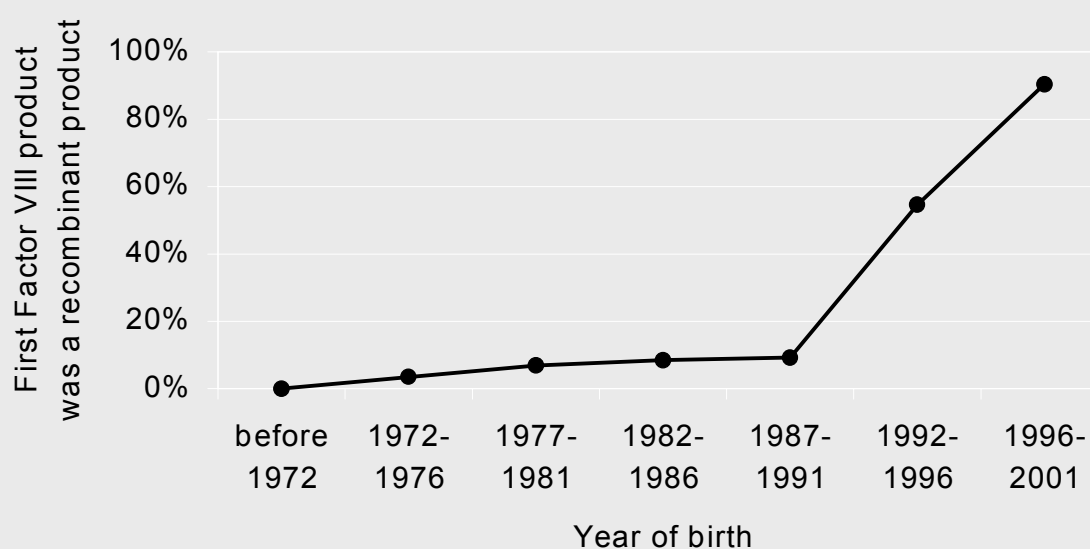
The total response to the questionnaire was 69% ( $n=1,084$ ). Respondents who were excluded from the analysis were patients who did not have hemophilia A ( $n =188$ ), patients who had not used FVIII in the past 1½ year ( $n=337$ , mainly mild hemophilia A), and patients for whom the type of first clotting factor used was not known ( $n=22$ ). In total, 537 respondents were eligible for analysis. Characteristics of the respondents are presented in Table 2.

**Table 2** Characteristics of the participants

|                                 | First use was rFVIII<br>(n=84) | First use was plasma<br>derived clotting factor<br>(n=453) |
|---------------------------------|--------------------------------|--|
| Mean age in years (95% CI)      | 9 (6-11)                       | 37 (35-38)   |
| Male                            | 84 (100)                       | 444 (99)   |
| Severity of disease             |                                |  |
| mild                            | 25 (31)                        | 85 (19)  |
| moderate                        | 16 (20)                        | 81 (18)  |
| severe                          | 41 (50)                        | 277 (63)   |
| Treatment modality              |                                |  |
| Home treatment                  | 27 (33)                        | 318 (72)   |
| Profylactic treatment           | 37 (45)                        | 234 (53)   |
| Infectious diseases             |                                |  |
| HIV positive                    | 0 (0)                          | 26 (6)   |
| Hepatitis C                     | 4 (5)                          | 284 (67)   |
| (Past) development of inhibitor | 5 (7)                          | 51 (13)  |
| Member of Hemophilia Society    | 72 (86)                        | 344 (77)   |
| High income                     | 39 (62)                        | 215 (52)   |
| High education                  | 30 (37)                        | 167 (39)   |

*All values are No. (%) except where otherwise indicated.  
95% CI=95% confidence interval*

First treatment had been with rFVIII for 16% ( $n=84$ ) of the participants, and with plasma derived clotting factor for 84% ( $n=453$ ). Because of the consensus among the Dutch hemophilia treaters to treat previously untreated patients (PUPs) with rFVIII, we expected that the large majority of respondents who started using clotting factor treatment after 1994 would start on rFVIII. As we did not have data on the year of first treatment, we used year of birth as a marker. Of all 537 respondents, 12% ( $n=67$ ) was born after 1994. In Figure 1 it can be seen that these respondents generally started on rFVIII.

**Figure 1** Percentage of respondents who started on rFVIII versus year of birth

### **Subsequent switch**

For the analysis of subsequent switching behaviour we included the 453 respondents whose first treatment had been with plasma derived clotting factors. Of these 45% ( $n=206$ , switchers) had switched from pdFVIII to rFVIII and 55% ( $n=247$ , nonswitchers) continued to use pdFVIII at the time of our questionnaire.

### **Patient characteristics**

The average age of the switchers (31 years, 95% confidence interval (CI) 28-33 years) was lower than of the nonswitchers (41 years, 95% CI 39-44 years). Switching was not associated with severity of disease, history of inhibitor formation, and home treatment (see Table 3). Respondents who had been infected with HIV or hepatitis C switched less to rFVIII than respondents who had not been infected ( $OR_{adj.}$  0.3, 95% CI 0.1-1.0). The fact whether respondents did or did not have family members who became infected with HIV or hepatitis C through the use of clotting factors, was not associated with switching behaviour. The more family members were using pd FVIII, the less the respondents themselves had switched from pdFVIII to rFVIII ( $OR_{adj.}$  0.7, 95% CI 0.5-0.9). On the other hand, the more family members were using rFVIII, the more the respondents had switched to rFVIII ( $OR_{adj.}$  2.7, 95% CI 1.6-4.3).

**Table 3** Univariate and multivariate logistic regression model of switching versus nonswitching

|  | <b>OR<sub>crude</sub></b><br><b>(95% CI)</b> |             | <b>OR<sub>adj.</sub>*</b><br><b>(95% CI)</b> |            |
|--|--|-------------|--|------------|
| <b>Parameters included in the multivariate model</b>                   |  |             |  |            |
| <i>Patient characteristics</i>   |  |             |  |            |
| Age  | 0.97   | (0.96-0.98) | 0.98   | (0.96-1.0) |
| HIV positivity   | 0.4  | (0.2-1.0)   | 0.3  | (0.1-0.9)  |
| Hepatitis C infection  | 0.4  | (0.3-0.6)   | 0.4  | (0.2-1.0)  |
| No. of family members on plasma  | 0.7  | (0.6-0.9)   | 0.6  | (0.5-0.9)  |
| No. of family members on recombinant                                   | 2.0  | (1.4-2.6)   | 2.7  | (1.6-4.4)  |
| Innovativeness (1-5)   | 1.3  | (1.0-1.8)   | 1.8  | (1.1-3.1)  |
| Prophylactic treatment   | 1.5  | (1.0-2.2)   | 1.4  | (0.7-2.8)  |
| Membership of Hemophilia Patients Society                              | 1.6  | (1.0-2.6)   | 1.4  | (0.6-3.4)  |
| Empowerment (1-4)  | 1.3  | (1.0-1.8)   | 1.2  | (0.7-2.1)  |
| High income  | 1.4  | (1.0-2.1)   | 1.4  | (0.8-2.7)  |
| <i>Treatment center</i>  |  |             |  |            |
| Size of treatment center (small/large)                                 | 5.6  | (2.6-12.2)  | 3.2  | (1.1-9.8)  |
| <i>Opinions</i>  |  |             |  |            |
| Pro-recombinant opinion (-30 through 30)                               | 1.1  | (1.1-1.2)   | 1.1  | (1.1-1.2)  |
| 'Never change a winning team' (1-5)                                    | 0.7  | (0.6-0.9)   | 0.8  | (0.6-1.1)  |
| Preference for a Dutch producer (1-5)                                  | 0.6  | (0.5-0.7)   | 0.8  | (0.5-1.1)  |
| Preference for not-for-profit producer (1-5)                           | 0.7  | (0.6-0.8)   | 0.8  | (0.6-1.1)  |
| <b>Other parameters from our prior model</b>                           |  |             |  |            |
| Severity of disease  | 1.1  | (0.9-1.4)   |  |            |
| (Past) development of inhibitor  | 1.5  | (0.8-2.7)   |  |            |
| Home treatment   | 1.4  | (0.9-2.2)   |  |            |
| No. of HIV positive family members                                     | 0.7  | (0.3-1.3)   |  |            |
| No. of family members with hepatitis C                                 | 1.2  | (0.8-1.8)   |  |            |
| High education   | 1.0  | (0.7-1.5)   |  |            |
| Agreement with 'Switching might cause problems, e.g. inhibitors' (1-5) | 0.9  | (0.8-1.2)   |  |            |

95% CI=95% confidence interval

\* Adjusted for all other parameters in the model

The three items on innovativeness (Cronbach's alpha 0.70), as well as the five items on empowerment (Cronbach's alpha 0.75) were clustered together in the analysis. In univariate analyses both were positively associated with switching from pdFVIII to rFVIII.

Membership of the Dutch Hemophilia Patients Society was also higher in the switchers than in the nonswitchers (81% versus 73%). Net income and education correlated only weakly (Cronbach's alpha 0.49), and therefore they were not clustered together as one measure of socio-economic status. In univariate analysis

high income was positively associated with switching, while high education was not. After adjustment for the other parameters in the model (see Table 3), the point estimates for the influence on switching of empowerment, income and membership of the Dutch Hemophilia Patients Society, and stayed very much the same, only the confidence intervals were broader. The influence of innovativeness increased after adjustment.

### *Influence of treating physician*

The 453 respondents were treated in 30 different treatment centers. Eighty-eight percent of the respondents were treated in 7 large centers (median number of respondents per center 31). In these large centers the percentage of respondents who had switched from pdFVIII derived to rFVIII varied from 26% to 71% (median 40%). In the small centers ( $n=23$ , median number of respondents per center 1) the percentage of switchers varied from 0% to 100% (median 0%). As such, being treated in a large hemophilia treatment center was positively associated with switching from pdFVIII to rFVIII ( $OR_{adj.} 3.2$ , 95% CI 1.1-9.8).

To the question who was the most influential in the choice of the type of FVIII product you are using, 54% of the participants answered 'my treating physician', 25% 'both me and my physician', and 21% 'me myself'. There was no difference between switchers and nonswitchers in this respect. Of the nonswitchers 44% of the respondents indicated that their physician had spoken with them about the choice between rFVIII and pdFVIII. Of the respondents who did discuss the topic with their treating physician (both switchers and nonswitchers), 79% indicated that it was their physician who brought up the topic. Only 21% initiated the conversation themselves. Of the nonswitchers who discussed product choice with their physician, 24% was advised to use pdFVIII, 8% to use rFVIII, and 68% to make their own decision. In the switchers these percentages were 1%, 52%, and 39% respectively.

### *Opinions*

Of the nonswitchers, 21% ( $n=45$ ) was thinking about switching to rFVIII in the future and 79% ( $n=167$ ) wanted to continue using pdFVIII. Forty percent of the switchers and 23% of the nonswitchers knew about the introduction of albumin-free formulations of rFVIII. Only 157 of the 453 participants gave an opinion on this development. Of these 157, 89% considered the introduction of albumin-free formulated rFVIII products either a small ( $n=52$ ) or a big ( $n=56$ ) improvement. Of the 45 nonswitchers who indicated to be thinking about switching to rFVIII, 21 (47%) did so since the introduction of the albumin-free formulations, and 25 (53%) already before this introduction.

The correlation between the two items measuring aversion against switching of clotting factor in general was too low to cluster them together in the analysis

(Cronbach's alpha 0.42). With the statement 'Switching from one clotting factor product to another may cause problems', most respondents, both switchers and nonswitchers, neither agreed nor disagreed. With the statement 'If you are doing well with your current treatment, you should never change to another clotting factor product', 39% of the switchers and 51% of the nonswitchers agreed.

Figure 2 shows how switchers and nonswitchers respectively, rated the importance of the 8 predefined product characteristics in choosing between rFVIII and pdFVIII. Overall, effectiveness and risk of infections were the most important characteristic. Switchers attached more weight to the risk of infections compared to nonswitchers, while nonswitchers attached more importance to effectiveness. Risk of inhibitor development and knowledge on long-term effects rank number 3 and 4 for switchers, and number 4 and 3 for nonswitchers, respectively.

The large majority of the participants (73%) considered rFVIII and pdFVIII equally effective (see Figure 3A). The remaining minority was divided: switchers believed rFVIII to be more effective, while nonswitchers believed the opposite. Also on the topic of inhibitor formation, the majority of the participants (57%) did not see a difference between rFVIII and pdFVIII. Thirty percent of the respondents were of the opinion that the antigenicity of pdFVIII is higher than of rFVIII. At this respect, there were no differences between switchers and nonswitchers (Figure 3B).

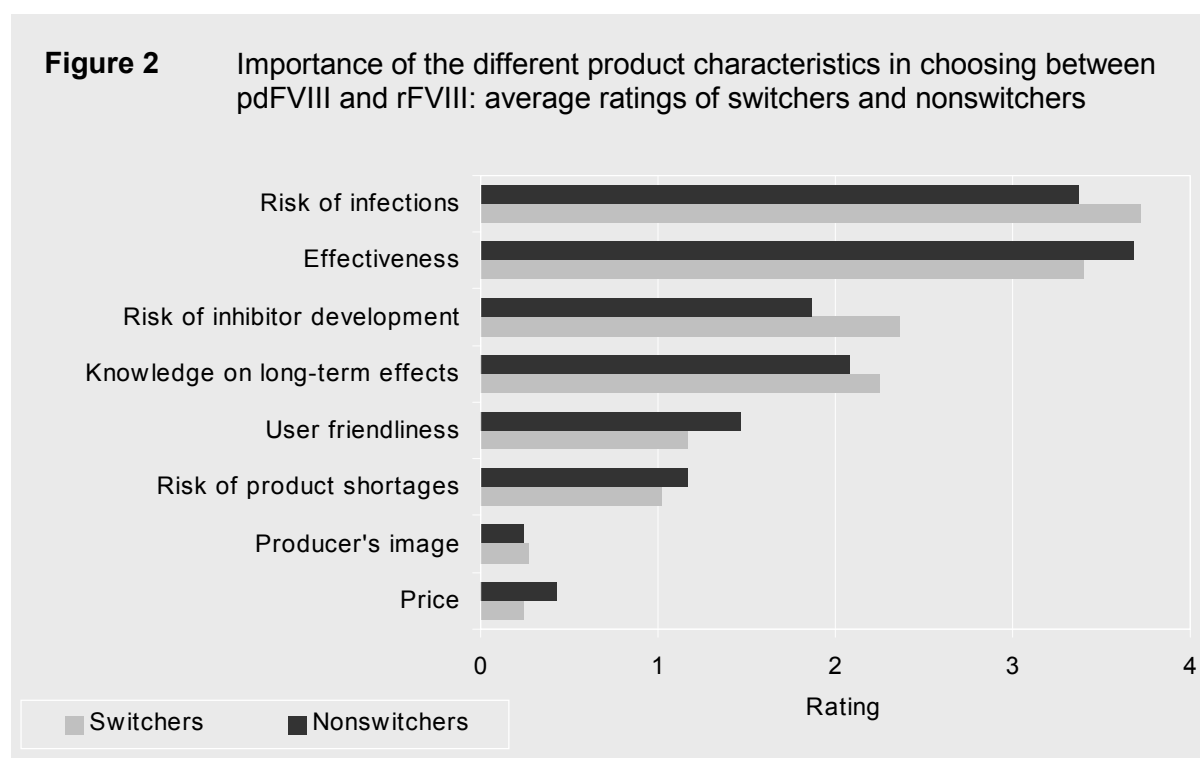
Eighty-four percent of the participants thought that the risk of infection is larger with pdFVIII than with rFVIII (Figure 3C). On the other hand, for rFVIII less knowledge is available about the long-term effects, was the opinion of 69% of the respondents (Figure 3D). Switchers answered these questions more in favour of rFVIII than nonswitchers did.

The large majority of the participants (67%) rated the image of the producers of rFVIII and of pdFVIII as equally good. To the remaining switchers the image of rFVIII producers was better, while the opposite was true for the remaining nonswitchers. Sixty-six percent of the switchers and 83% of the nonswitchers agreed with the statement 'I prefer to use FVIII from a Dutch producer over FVIII from a foreign producer' (see Figure 3E). Similarly, 50% of the switchers and 67% of the nonswitchers agreed with the statement 'I prefer to use FVIII from a not-for-profit producer over FVIII from a for-profit producer' (Figure 3F).

On the topic of user friendliness, the majority of the participants, 58% of switchers and 78% of nonswitchers respectively, did not see a difference between rFVIII and pdFVIII. The remaining minority was divided: switchers more in favour of rFVIII and nonswitchers more in favour of pdFVIII.

With respect to the risk of product shortages, the participants were divided: 26% thought that shortages are more likely for rFVIII products than for pdFVIII, while 42% thought the other way around. There was no difference between switchers and nonswitchers on this topic.





To the question 'Have you been troubled by shortages of FVIII product during this year or last year (2000+2001)?' 27% ( $n=56$ ) of switchers and 7% ( $n=16$ ) of nonswitchers answered in the affirmative.

The summarised score for respondents' opinions on product characteristics was 6 (95% CI 5-7) for switchers, and -0.3 (95% CI -1 - 1) for nonswitchers.

## DISCUSSION

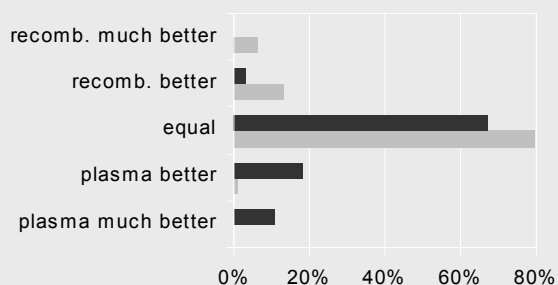
Approximately 6 years after its introduction, 54% of recent FVIII users in the Netherlands used rFVIII. From 1995 onwards, nearly all children who had to be treated with FVIII for the first time (PUPs), were prescribed rFVIII. From all respondents who had started using pdFVIII in the past, 45% switched to rFVIII and 55% continued using pdFVIII at the time of our questionnaire.

The percentage of respondents who had switched from pdFVIII to rFVIII varied from 0% to 100% in small centers and from 26% to 71% in large centers. From this large variability one may conclude, that the treating physician strongly influences product choice. This conclusion is further strengthened by the fact that only 21% of the respondents regarded themselves as the most influential person in choosing a certain type of clotting factor and 54% indicated their doctor as such.

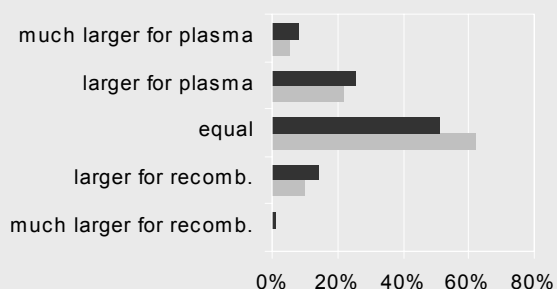
Nevertheless, the fact that innovativeness, opinion on rFVIII, and the type of product family members are using, are associated with switching behaviour, may confirm the hypothesis that there is a patient influence, as well.

**Figure 3** Opinions of switchers and nonswitchers on various topics

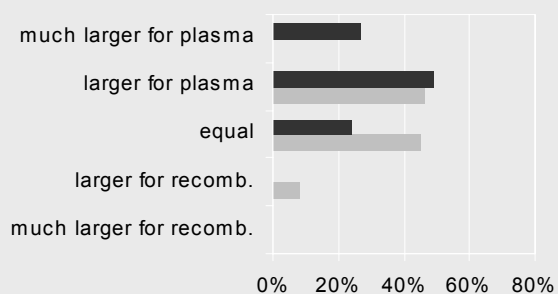
**Figure 3a** Effectiveness



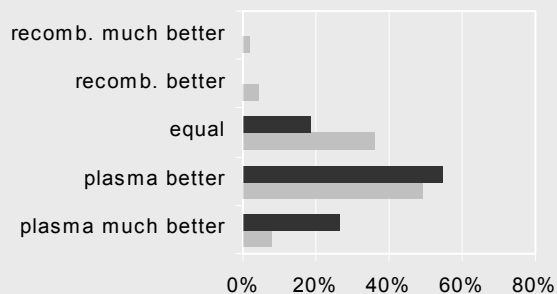
**Figure 3b** Risk of inhibitor formation



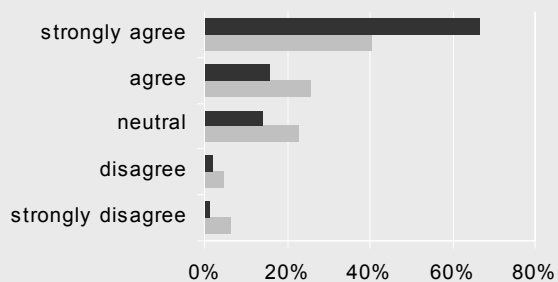
**Figure 3c** Risk of infections



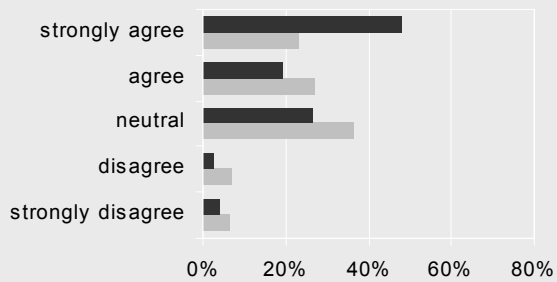
**Figure 3d** Knowledge on long-term effects



**Figure 3e** I prefer a Dutch producer over a foreign producer



**Figure 3f** I prefer a not-for-profit over a for-profit producer



■ Switchers ■ Nonswitchers

Here, however, the cross sectional characteristic of our data complicates interpretation of the results. We cannot determine whether a favourable opinion on rFVIII caused people to switch, or whether the switch caused the favourable opinion. The same holds true for the influence of family members using a certain type of product. Innovativeness, however, is an independent patient characteristic, and as such its association with switching behaviour does show that the patients themselves also have a say in the choice between pdFVIII and rFVIII.

We also cannot firmly conclude whether age, HIV infection, and hepatitis C infection are associated with switching behaviour through physicians' policies or through patient preferences. As there are no treatment guidelines in the Netherlands indicating that HIV negatives or younger people should preferentially be treated with rFVIII, the mechanism through patient preferences is the most likely. Probably, younger people are more willing or demanding to switch to a new treatment than older people are. We found no significant difference between HIV positives and HIV negatives with regard to their opinion on the risk of infections for rFVIII compared to pdFVIII. However, the number of HIV positives ( $n=26$ ) was small and they constituted a selected group as many HIV positives have died already.

There seems to be a weak association between preferring a Dutch, or a not-for-profit producer, and continued use of pdFVIII. Since pdFVIII is available from a non-for-profit Dutch producer, and rFVIII is not, this association seems logical. As there are no clear guidelines on which patients to switch from pdFVIII to rFVIII, we hypothesised that physicians mainly switched those patients to rFVIII who especially asked for it, which we expected to be the most empowered patients, members of the Dutch Hemophilia Patients Society, or patients with a higher social economic status. Except for the absence of an effect of high education, our hypothesis is indeed confirmed by the data. This, again, points in the direction that the patient does play a part in the adoption of rFVIII as well, in addition to the strong influence of the treating physician.

After the many years of discussion about the perceived increased antigenicity of rFVIII, it is remarkable that only 13% of the respondents thought rFVIII to be more antigenic than pdFVIII. Generally the respondents do not see large differences between rFVIII and pdFVIII, except for the risk of infections (larger for pdFVIII) and the knowledge on long-term effects (larger for pdFVIII, as well).

Given that the Dutch hemophilia treaters prescribe rFVIII to all incident users, why do they not convert all prevalent patients from pdFVIII to rFVIII, as well? One often heard answer is that the supply of rFVIII would not be sufficient. Although, there indeed was a shortage of rFVIII at the time of our questionnaire, the validity of this answer may be questioned, as countries like Denmark and Scotland did succeed in switching all their hemophilia patients from pdFVIII to rFVIII in response to the Bovine Spongiform Encephalopathy (BSE) crisis [19]. Our current study provides insight only in the opinions of hemophilia patients. It would be very worthwhile to study hemophilia treaters as well. Although hemophilia patients may well represent one of the most empowered and well informed patient groups, our results suggest that, nevertheless, physicians are a major influence in the relatively slow diffusion of rFVIII.

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# 8

## **The diffusion of recombinant Factor VIII: a study of physicians' preference**

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*Submitted for publication*

**ABSTRACT**

*Aim and methods* - The diffusion of recombinant Factor VIII (rFVIII) has been relatively slow in the Netherlands. In a previous study among hemophilia patients we found that physicians play an important part in the choice between plasma derived Factor VIII (pdFVIII) and rFVIII. The objective of the current study was to investigate the opinions of hemophilia treating physicians on this topic.

*Results* - On average, the physicians prescribed rFVIII to 56% of their patients. This percentage varied widely between centers. Only one doctor would choose to use pdFVIII if he would suffer from hemophilia A himself and 74% would choose to use rFVIII. Previously untreated patients were preferentially treated with rFVIII by 95% of the physicians, and young patients by 81%. HIV status, severity of the disease, prophylaxis, and type of product used by family members were no reasons for most physicians to change their advice.

## **INTRODUCTION**

In 1995, recombinant Factor VIII (rFVIII) was introduced in the Netherlands for the treatment of patients with hemophilia A, as a possible substitute for plasma derived Factor VIII (pdFVIII). Now, six years later, rFVIII is used by about 50% of the Dutch patients, while the other 50% continue to use pdFVIII [1]. Compared to other biotechnology substitutions, the diffusion of rFVIII is relatively slow. In the Netherlands, both recombinant human growth hormone and recombinant human insulin quickly reached a complete replacement of their organic counterparts, and the recombinant follitropins have captured an 80% market share within 4 years [2-4]. Also in comparison to other countries, the diffusion of rFVIII in the Netherlands has been slow. Ireland, Scotland and Denmark have completely switched from plasma derived to rFVIII as a matter of health policy [5]. In France rFVIII represents 80% of all FVIII used [6], and in Germany it represents 50% [7].

In a previous study, we investigated determinants of the diffusion of rFVIII, by use of a postal questionnaire among Dutch hemophilia patients. We found that from 1995 onwards, nearly all children who had to be treated with FVIII for the first time (previously untreated patients, PUPs), were prescribed rFVIII. Older age, human immunodeficiency virus (HIV) positivity, infection with hepatitis C, and having family members who use pdFVIII, were negatively associated with switching from pdFVIII to rFVIII. A positive attitude towards innovations, a positive opinion on rFVIII, and having family members who use rFVIII, were positively associated with switching. In addition, there was a strong influence of the center in which patients were treated. The proportion of patients who had switched from pdFVIII to rFVIII varied from 0% to 100% in the small centers, and from 26% to 71% in the large centers. Only 21% of the patients considered themselves as the most influential person in choosing a certain type of clotting factor, while 54% considered their physician to be this person.

The objective of the current study was to investigate the opinions of hemophilia treating physicians on the choice between pdFVIII and rFVIII. The outcomes were compared with the outcomes from our previous study in patients.

## **METHODS**

### ***Mailing procedure***

In May 2001, we sent a postal questionnaire to the 26 directors of the licensed hemophilia care centers in the Netherlands. Additional questionnaires were included, which they were asked to distribute among the colleagues in their department who autonomously treated hemophilia patients as well. To enable us to measure the response, we requested the directors to report to how many of their colleagues they had given a questionnaire. Reminders were sent after two weeks.

### **Content**

The additional questionnaires for the colleagues were identical to the directors' questionnaires, except that only the directors were asked to fill the characteristics of their department's patient population: number of patients with hemophilia A and B, severity, number of patients on plasma derived and on recombinant clotting factors, number of patients with inhibitors and number of infections with HIV and hepatitis C.

The questionnaire for doctors was based on the questionnaire we developed for patients. To enhance comparability the following items have been copied from the patient's questionnaire: aversion against switching, most important influence in clotting factor choice (physician himself, the patient, or both equally influential), preference for a specific producer (Dutch over foreign, not-for-profit over for-profit), and opinion on albumin-free formulations of recombinant Factor VIII. The items on aversion against switching were located at the beginning of the questionnaire, before the issue of recombinant versus plasma derived clotting factors was introduced. Also, we copied the question where, from a list of eight (price, effectiveness, user friendliness, producer's image, knowledge on long-term effects, risk of infections, risk of product shortages and risk of inhibitor formation), respondents were asked to indicate which they found the five most important characteristics. Their opinion on the eight characteristics was asked on a 5-points scale (-2 very favourable for plasma, -1 favourable for plasma, 0 the same for plasma and recombinant, 1 favourable for recombinant, 2 very favourable for recombinant).

We also included specific questions on the personal characteristics of the responding doctor, such as age, sex, year of graduation from medical school, medical specialism, and whether they treated mainly adults, children, or both. In addition, the respondents were asked which type of clotting factor they would choose for themselves if they had severe hemophilia (plasma derived, recombinant or no preference). Before the questionnaire was actually sent out, two doctors were asked to complete the questionnaire and to give their comments. This 'pilot' was helpful in optimising the structure and the content of the questionnaire.

### **Analysis**

To calculate the response, we assumed that directors who, after the reminder, did not respond to our questionnaire, had not distributed it among colleagues either. The departments were categorised into three groups: departments treating mainly adults, departments treating mainly children, and departments treating both. Personal characteristics of the respondents were described, as were the influences of patient characteristics on the doctor's advice about rFVIII versus pdFVIII. The personal opinions of doctors on matters related to the choice between pdFVIII and rFVIII were described and were compared with the opinions patients expressed in our



previous study. Details about this study, including the mailing procedure and the content of the questionnaire, have been described in the previous chapter.

## **RESULTS**

### ***Response and participants***

Eighteen directors returned the questionnaire (response 69%). They reported that they had forwarded the questionnaire to 18 colleagues. Overall, including colleagues, we received 30 filled-out questionnaires (response 30/44=68%). Together, the directors reported to take care of 1,316 patients with hemophilia A and 169 patients with hemophilia B. As such, our sample represents the treating physicians of >95% of all Dutch hemophilia patients. One director was excluded because he did not see hemophilia patients anymore. A total of 29 participating physicians, from 17 departments, remained for analysis.

Mean age of the respondents was  $47 \pm 3$  years. Fifty-nine percent was male, and the average year of graduation from medical school was 1980. Seven percent ( $n=2$ ) were MDs, 11% ( $n=3$ ) internists, 46% ( $n=13$ ) hematologists, 21% ( $n=6$ ) pediatricians, and 14% ( $n=4$ ) pediatric hematologists.

### ***Departments***

In total, the 17 departments took care of 1,236 FVIII users, 696 of which were using rFVIII (56%). However, this percentage varied widely between the departments. In the departments where they treated mainly adults ( $n=8$ ; 501 patients), the proportion of patients using rFVIII ranged from 0 to 75% (median 12%), and in the departments where they treated mainly children ( $n=6$ ; 167 patients), it varied between 0 and 100% (median 84%). On average the proportion of patients using rFVIII was 2.9 times higher in departments treating children than in departments treating adults ( $p=0.02$ ).

### ***Patient characteristics***

Seventy percent of the 29 physicians indicated that they had discussed the choice between pdFVIII and rFVIII with all their patients. When asked on whose initiative their patients had generally switched from pdFVIII to rFVIII, 11% of the doctors answered that this had been on the initiative of the patient, 44% answered it was their own initiative (the physician's), 30% answered that it varied, and 15% answered that none of their patients switched from pdFVIII to rFVIII. Only one respondent indicated the patient to be the most influential in choosing a FVIII product, 41% ( $n=11$ ) indicated themselves (the physician), and 56% ( $n=15$ ) said both were equally influential.

**Table 1** To which patients do you tend to advise rFVIII instead of pdFVIII?  
Results are given in percentages ( $n=22$ ).

| Patient characteristic                       | Doctor's preference to advise rFVIII instead of pdFVIII |                      |   |
|--|---|----------------------|---|
|  | severe hemophiliacs                                     | no preference        | mild hemophiliacs                                 |
| <b>Severity of the disease</b>               | 14  | 76                   | 10  |
| <b>Previously un-treated patients (PUPs)</b> | PUPs<br>95  | no preference<br>5   | previously treated patients<br>0                  |
| <b>Age</b>                                   | young patients<br>81                                    | no preference<br>19  | old patients<br>0                                 |
| <b>HIV</b>                                   | HIV positives<br>15                                     | no preference<br>55  | HIV negatives<br>30                               |
| <b>Prophylaxis</b>                           | patients on prophylaxis<br>5                            | no preference<br>91  | patients not on prophylaxis<br>5                  |
| <b>Home treatment</b>                        | patients on home treatment<br>0                         | no preference<br>100 | patients not on home treatment<br>0               |
| <b>Family members using rFVIII</b>           | patients with family members using rFVIII<br>24         | no preference<br>76  | patients without family members using rFVIII<br>0 |
| <b>Compliance</b>                            | compliant patients<br>5                                 | no preference<br>95  | non-compliant patients<br>0                       |
| <b>Inquirement</b>                           | patients who do inquire about rFVIII<br>10              | no preference<br>90  | patients who do not inquire about rFVIII<br>0     |
| <b>Fear for BSE</b>                          | patients afraid of BSE<br>29                            | no preference<br>71  | patients not afraid of BSE<br>0                   |

*HIV=Human Immunodeficiency Virus, BSE=Bovine Spongiform Encephalopathy*

Five doctors (17%) gave the same advice to all patients: one advised all his patients to use pdFVIII, two advised all their patients to use rFVIII, and two remained neutral and had their patients decide for themselves. The remaining 22 doctors gave differential advices. The reasons given for this were the limited availability of rFVIII (23%), differences between patients (32%), or both (46%).

The 22 doctors who gave differential advices were asked to which patients they tended to advise rFVIII instead of pdFVIII. The results are shown in Table 1.

Young patients were preferentially treated with rFVIII by 81% of the respondents, and PUPs by 95%. Thirty percent preferred to give rFVIII to HIV negative patients. Twenty-nine percent of the doctors were more inclined to advise rFVIII to patients who were afraid of BSE than to patients who were not afraid of BSE. Twenty-four percent took in consideration whether family members of the patient were already using rFVIII.

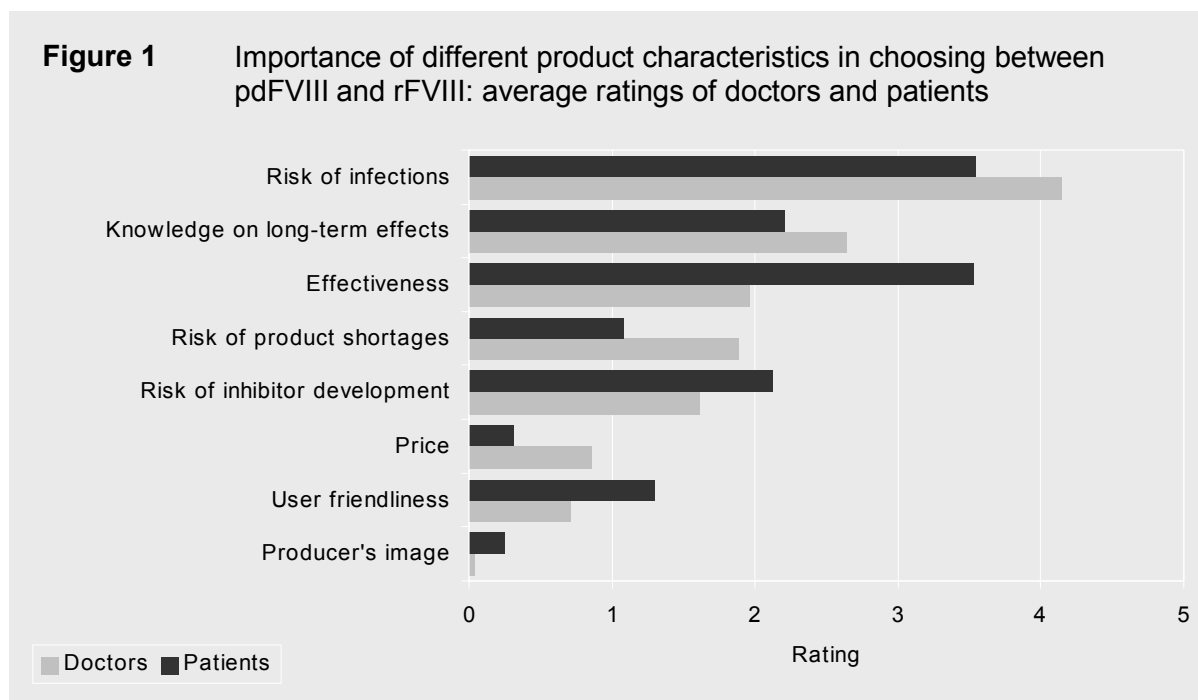
### **Opinions**

Figure 1 shows how doctors and patients rated the importance of the eight predefined product characteristics in choosing between different clotting factor products. The average rating for a product characteristic could be 5 at the most and 0 at the least. Risk of infections and knowledge on long-term effects were the most important characteristic. Risk of product shortages and of inhibitor development ranked number 3 and 4.

With regard to the transmission of infections, most doctors believed that the risk is greater with pdFVIII as compared to rFVIII (Figure 2A). However, knowledge on long-term effects is better on pdFVIII, was the opinion of the majority of the physicians (Figure 2B). All doctors were of the opinion that rFVIII and pdFVIII are equally effective. Also on the topics of inhibitor formation (Figure 2C), user friendliness, and producer's image, doctors did not see a difference between pdFVIII and rFVIII. As can be seen in Figure 2D, opinions on the risk of product shortages were very much divided. The summarised score for the physicians' opinions on product characteristics was -0.6 (95% CI -2.0 – 0.1). If the doctors would suffer from severe hemophilia A themselves, 74% would choose to use rFVIII, 4% pdFVIII, and 22% had no preference.

Most doctors neither agreed nor disagreed with the statement 'I prefer to use FVIII from a Dutch producer over FVIII from a foreign producer'(Figure 2E). The physicians were either neutral or had a preference for a not-for-profit provider (Figure 2F). With the statement 'Switching from one clotting factor product to another may cause problems', most doctors (48%) disagreed (Figure 2G). With the statement 'If you are doing well with your current treatment, you should never change to another clotting factor product'(the notion to never change a winning team), 38% of the doctors (Figure 2H).

In 2000, two virtually albumin-free formulations of rFVIII (Kogenate Bayer® and Helixate NexGen®) were introduced. They contain 1000 times less plasma derived albumin than the former formulations, and have an additional detergent based purification step, further reducing the potential for virus transmission [8]. Twenty-six of the 29 doctors (90%) knew about the introduction of albumin-free formulations of rFVIII.



Twenty-one considered it an improvement (81%), while 5 thought it made no difference. The introduction of albumin-free formulations of rFVIII did not influence the policy of 89% of the doctors; only 11% started to prescribe more rFVIII.

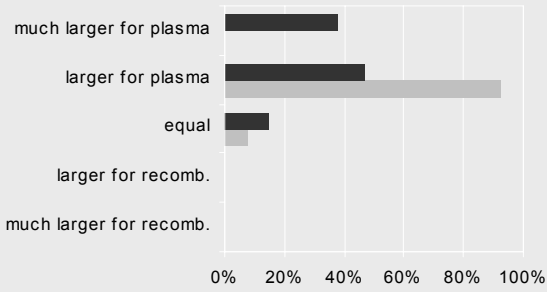
## DISCUSSION

On average, the physicians prescribed rFVIII to 56% of their patients. This percentage varied tremendously between departments, both within the group of departments treating mainly children, as well as within the group of departments treating mainly adults. Unfortunately, the number of departments was too small to use multiple linear regression and to investigate whether the opinions or the innovativeness of the physicians within a department were predictive of the proportion of patients on rFVIII.

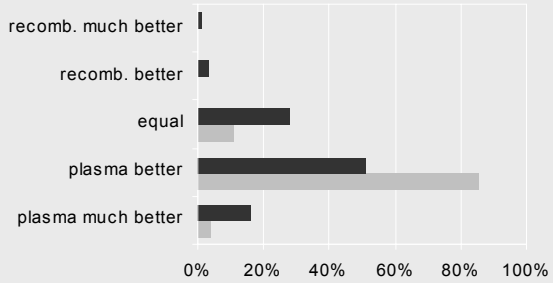
According to expectations, PUPs were preferentially treated with rFVIII by 95% of the physicians. In the study among patients we found that, even when PUPs were excluded, people of younger age were more likely to have switched from pdFVIII to rFVIII than people of older age. Here, 81% of the physicians confirmed that they tend to advise rFVIII more often to younger patients than to older patients. As a result, the proportion of patients using rFVIII was on average 2.9 times higher in departments treating mainly children than in children treating mainly adults. In our study among patients HIV positivity was negatively associated with switching from pdFVIII to rFVIII.

**Figure 2** Opinions of doctors and patients on various topics

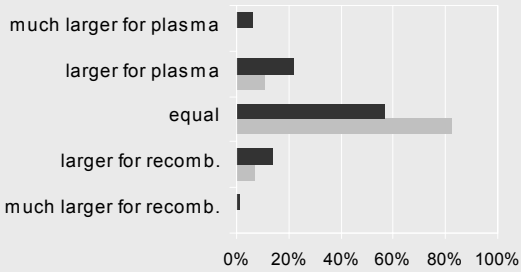
**Figure 2a** Risk of infections



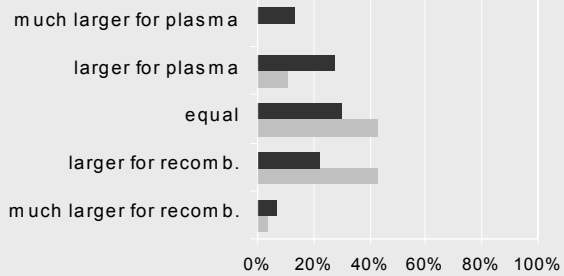
**Figure 2b** Knowledge on long-term effects



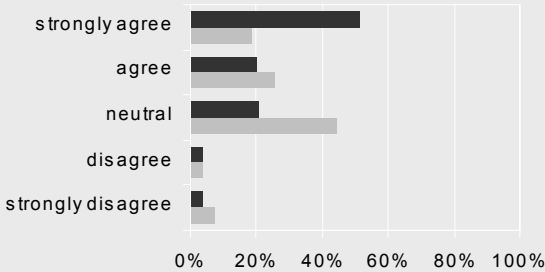
**Figure 2c** Risk of inhibitor formation



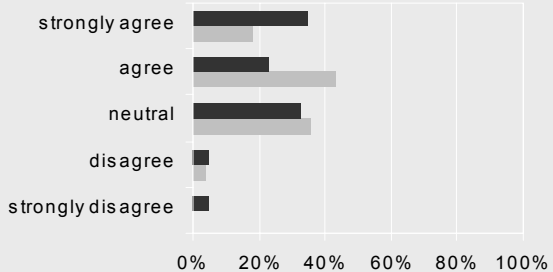
**Figure 2d** Risk of product shortages



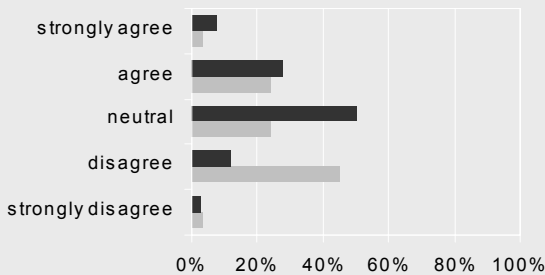
**Figure 2e** I prefer a Dutch producer over a foreign producer



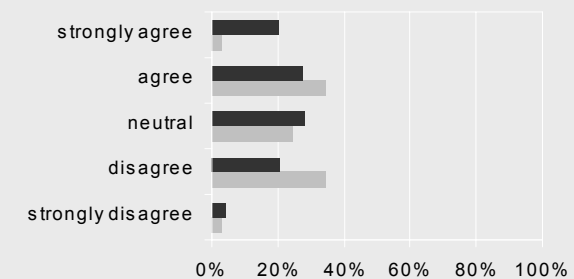
**Figure 2f** I prefer a not-for-profit over a for-profit producer



**Figure 2g** Switching may cause problems, e.g. inhibitor formation



**Figure 2h** 'Never change a winning team'



Doctors Patients

The current study among physicians showed that for most doctors HIV positivity was not a reason to advise pdFVIII. Therefore, the association must go largely through patient preferences. Similarly, the influence of the product choice of family members must be explained by patients' preferences, as only 24% of the doctors' indicated that this was a reason for them to adjust their advice.

The doctors' ranking of the importance of eight predefined product characteristics was quite similar to that of the patients. On average, the doctors valued the difference in risk of infections between rFVIII and pdFVIII as smaller than the patients did. Also, the knowledge on long-term effects and the risk of product shortages were assessed more in favour of pdFVIII by doctors than by patients. Overall, doctors were less in favour of rFVIII than patients were (summarised score -0.6 versus 3.0). Still, if they had suffered from hemophilia A themselves, only one doctor would choose to use pdFVIII, and 74% would choose to use rFVIII.

Sixty-eight percent of the 22 doctors who gave different advices to different patients, indicated that they did so, among other things, because of the limited availability of rFVIII. In the preparatory interviews, which we conducted to construct the questionnaire for patients, we learned that the hemophilia treating physicians, united in the Dutch Hemophilia Treatment Society, had agreed upon the launch of rFVIII to introduce this new product very gradually to build up experience and to minimise the risk of shortages. They reasoned that a sudden and complete switch to rFVIII, would mean the end of the production of pdFVIII by the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB), the major provider of plasma derived FVIII (pdFVIII) in the Netherlands. They preferred to keep both the CLB and the producers of rFVIII into business, as history had learned that dependence on a single producer makes one vulnerable. It turns out that physicians have indeed adhered to this agreement.

In conclusion, the decision of physicians united in the Dutch Hemophilia Treatment Society to introduce rFVIII only gradually has greatly influenced the diffusion of rFVIII in the Netherlands. The physicians decided to preferentially prescribe rFVIII to all PUPs, and this agreement was largely followed. Beside this, they left room to switch some, but not all patients from pdFVIII to rFVIII. Only in this part patient preferences do come into play.

### **ACKNOWLEDGEMENTS**

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# 9

## **From human menopausal gonadotropins (hMG) through purified urinary follicle stimulating hormone (FSH) preparations to recombinant FSH: a substitution study**

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## ABSTRACT

*Aim and methods* - Drugs produced through the use of recombinant DNA techniques have become an integral part of medical practice. Before recombinant Follicle Stimulating Hormone (rFSH) was introduced in 1996, FSH purified from the urine of postmenopausal women had been commercially available since the 1960s. We analysed the diffusion and the substitution patterns of the different FSH preparations in the Netherlands.

*Results* - The fact that rFSH preparations have batch-to-batch consistency, are free from urinary protein contaminants and have the potential to be produced in limitless quantities, is advantageous. The question whether newer, more pure FSH products are beneficial from the clinical perspective, has not been settled without reasonable doubt. The price of rFSH is three times as high as the price of the former FSH preparations. Due to the introduction of rFSH, total FSH expenditures have grown from €5.0 million in 1995, to €26.8 million in 2000, while the volume increased by less than 100%. Both the pharmaceutical companies and the payers (government, insurers) have influenced the patterns of substitution of existing FSH products by biotech equivalents.

*Conclusion* - In general, the risk of increasing pharmaceutical costs without clear clinical benefits has so be set against the risk of strangling innovations. Therefore, a continuous process of technology assessment is necessary.

## **INTRODUCTION**

Since 1982, with the advent of recombinant human insulin, biotechnology drugs produced through the use of recombinant DNA techniques have become an integral part of medical practice. However, this has not happened without striking a blow. As McKelvey described in her book on the development of recombinant human growth hormone, biotechnology as a new means to produce pharmaceuticals initially could not always count on a warm welcome [1]. Public opinion on biotechnology is still not entirely positive, although most opposition is directed at its application in the food industry. At the same time, high expectations have been placed on the young biotech industry since its emergence in the 1980s. The euphoria subsided somewhat during the 1990s, but at the beginning of this century, with the completion of the Human Genome Project promises rose again. With pharmaceutical recombinant proteins being around for almost 20 years, the question of how these products are taken up in medical practice can now be raised.

In this paper we describe and analyse the case of one specific biotechnology drug, namely recombinant Follicle Stimulating Hormone (rFSH) and its diffusion into Dutch medical practice. This case touches on a topic which has previously been identified as an important issue in the assessment of biotechnology drugs, namely that rFSH constitutes an alternative option for already existing medicines purified from an organic source [2]. FSH extracted from the urine of postmenopausal women has been commercially available already since the 1960s, before rFSH was introduced in 1996. Similarly insulin, growth hormone, and clotting Factor VIII, respectively derived from animal pancreas, human pituitary tissue and plasma from blood donors, had already been in use long before the recombinant versions of these products became available. In this study we will depict the diffusion patterns of the different FSH preparations and the consequences of the introduction of the recombinant products. Data on the sales of FSH products were kindly provided to us by two of the pharmaceutical companies involved. Information on pivotal articles published, product introductions and withdrawals, reimbursement decisions, and the like, will be examined along with diffusion data to obtain insight in the processes underlying the adoption of these products by clinical practice.

### ***FSH and in vitro-fertilisation (IVF)***

FSH containing gonadotropin preparations have been commercially available since the 1960s. Their first use was in ovulation induction in women with anovulatory disorders. Since 1978, however, when the first IVF baby was born, they have been used increasingly in assisted reproductive technologies such as IVF and intra uterine insemination (IUI). Now, ovulation induction comprises only 10% of gonadotropin usage, while 90% is used for ovarian hyperstimulation in assisted reproductive technologies (about half for IVF and half for IUI in stimulated cycles) [3].

In the Netherlands, a total of 200,000 babies are born each year and 1 in 70 of them is conceived using IVF techniques [4]. IVF starts with ovarian hyperstimulation using gonadotropins preparations, containing FSH alone, or combined with luteinising hormone (LH). In the normal menstrual cycle out of a cohort of 10-20 antral follicles only one obtains dominance over the others and shows continued growth until ovulation takes place. In IVF, through the administration of FSH (for on average 10 days, starting on day 2-3 of the menstrual cycle), the maturation of a larger part of the antral follicle cohort is aimed for. During the stimulation phase pituitary desensitisation with a Gonadotropin-Releasing Hormone (GnRH) agonist is accomplished to prevent premature LH activity and ovulation. Those follicles that will grow up till the preovulatory stage, will then be exposed to a surrogate midcycle LH peak (by using exogenous human Chorion Gonadotropin) and be punctured under transvaginal ultrasound observation in order to harvest the oocytes contained in the follicles (oocyte retrieval). In the laboratory the oocytes will be fertilised and, after in vitro culture for 3 to 4 days, transferred into the uterus, at which time the embryos will be at the 8 to 64 cell stage (embryo transfer).

### **Products**

FSH containing gonadotropin preparations can be divided into 4 groups (see Table 1): 1) human Menopausal Gonadotropins (hMG), containing both FSH and LH; 2) urinary FSH (uFSH); 3) highly purified urinary FSH (uFSH-HP); and 4) recombinant FSH (rFSH). Both hMG and uFSH contain a lot of, mainly undefined, urinary protein contaminants, rendering their purity less than 5%. Through the application of immunochromatography with monoclonal antibodies against FSH, an increased purity of more than 95% is achieved in uFSH-HP preparations. Because of the increased purity, both uFSH-HP and rFSH can be administered subcutaneously as well as intramuscularly.

Urinary derived preparations contain both intact FSH dimers as well as inactive FSH subunits. As such, mass is not a good indicator of urinary FSH content and the amount of gonadotropins in each product is usually expressed in international units (IU) of FSH activity, as measured in a standardised bioassay.

Although both FSH and LH are required for normal follicular growth and maturation, the precise role of LH is at present still uncertain. Since it was shown in the late 1980s that too high concentrations of LH might have negative effects on fertilisation and embryo quality, the idea arose that pure FSH preparations might be superior to hMG preparations [5,6]. This hypothesis was tested in several clinical trials comparing uFSH with hMG with respect to pregnancy rates per IVF treatment cycle. Statistical significance was not reached in any of these individual studies [5,6]. However, in 1995 a meta-analysis by Daya et al.[5] was published, which included 8 studies and demonstrated a significant difference in favour of uFSH (see Table 2).

**Table 1** FSH containing gonadotropin preparations on the Dutch market

|                | <b>hMG</b>  | <b>uFSH</b>                             | <b>uFSH-HP</b>   | <b>rFSH</b>   |
|----------------|---|---|--|---|
| Full name      | human menopausal gonadotropins  | urinary FSH                             | highly purified urinary FSH  | recombinant FSH   |
| Source         | urine from post-menopausal women  | urine from post-menopausal women        | urine from post-menopausal women   | genetically modified cells from Chinese hamster ovary                                 |
| Ingredients    | FSH + LH  | FSH                                     | FSH  | FSH   |
| Purity         | <5%   | <5%                                     | >95%   | 99%   |
| Administration | i.m.  | i.m.                                    | i.m. or s.c.   | i.m. or s.c.  |
| Brands         | Humegon <sup>®</sup><br>(1963, Organon)<br>Pergonal <sup>®</sup><br>(1970, Serono)<br>Menogon <sup>®</sup><br>(1997, Ferring) | Metrodin <sup>®</sup><br>(1986, Serono) | Metrodin HP <sup>®</sup><br>(1995, Serono)<br><br>Follegon <sup>®</sup><br>(1995, Organon) | Gonal-F <sup>®</sup><br>(1996, Serono)<br><br>Puregon <sup>®</sup><br>(1997, Organon) |

A few years later this finding was contradicted by a meta-analysis by Agrawal et al.[6], who argued that meta-analyses should take into account the different pituitary desensitisation protocols used. When pooling together 11 trials with the most commonly used GnRH agonist protocol (the long protocol), the overall odds ratio for comparing FSH and hMG was not significant. Although this meta-analysis was criticised on the issue of study selection bias, re-analysis following the inclusion and exclusion of selected studies did not change the overall results of the study [7-9].

A second issue that has been addressed in scientific literature, is the comparison between rFSH and urinary FSH (uFSH or uFSH-HP). The fact that recombinant preparations have batch-to-batch consistency, are free from urinary protein contaminants and have the potential to be produced in limitless quantities is advantageous. The question whether rFSH also leads to more clinical pregnancies per IVF cycle has been addressed by several clinical trials, none of which reached statistical significance. However, two meta-analyses pooling together the results of several trials, did show significant treatment effects in favour of rFSH [10,11]. The interpretation of these meta-analyses is still debated, since they compare two types of rFSH (the alpha and beta variant), as well as different types of urinary FSH (uFSH and uFSH-HP, and in Out's meta-analysis one study with hMG was also included). In Daya's analysis, which received Cochrane status, an absolute increase in pregnancy rates of 3.7% (95% confidence interval (CI) 0.5-6.9%) was demonstrated comparing rFSH to uFSH/uFSH-HP (see Table 2).

| <b>Meta-analysis</b>                | <b>Preparations compared</b> | <b>No. of trials included (period)</b> | <b>Pregnancies per cycle (confidence interval)</b> | <b>p</b>       |
|-------------------------------------|------------------------------|--|--|----------------|
| Daya et al., (1995)                 | uFSH<br>hMG                  | 8 ('86-'94)                            | OR=1.71<br>RD=8.5%                                 | 0.013<br>0.009 |
| Out et al., (1997)                  | rFSH<br>uFSH / hMG           | 3 ('95-'96)                            | -<br>RD=4.9% (0.1 – 9.6 %)                         | -<br>0.044     |
| Daya et al., (1999)                 | rFSH<br>uFSH / uFSH-HP       | 12 ('93-'98)                           | OR=1.2 (1.02 – 1.42)<br>RD=3.7% (0.5 – 6.9 %)      | 0.03<br><0.05  |
| Agrawal et al., (2000) <sup>†</sup> | uFSH<br>hMG                  | 11 ('93-'97)                           | OR=0.77 (0.58 – 1.05)                              | 0.76           |

<sup>†</sup> Only the meta-analysis for trials using the long protocol for gonadotropin-releasing hormone (GnRH) analogs is included.  
OR=odds ratio; RD= absolute risk difference

Clinical pregnancy rates are influenced by the fact that in most IVF clinics only a limited (usually 2-3) number of embryos are transferred into the uterus to prevent large multiple pregnancies. The surplus of embryos usually is frozen, and subsequently they can be thawed and used in another IVF cycle without follicular stimulation (cryopreservation). Therefore, it has been suggested that the number of oocytes retrieved or the number of cumulative pregnancies, including those from frozen-thawed embryo transfer cycles, might be more appropriate endpoints. Oocyte retrieval was shown to be significantly higher for rFSH compared to uFSH/uFSH-HP in several individual trials [12-15]. The reason for this is not yet fully understood [14]. With regard to cumulative pregnancy rates including cryopreservation, a significant difference in favour of rFSH has been shown in one large trial by Out et al.[12]. In many other trials [13-15] and in the latest meta-analysis by Daya et al. [11] this endpoint was not addressed. The long-term effects of IVF on the growth and development of derived children are not yet totally clear. Cryopreservation and thawing involve major cellular changes and may cause (additional) adverse effects. Although the limited data available on this topic are reassuring, more data are needed to be able to weigh the advantages of using cryopreserved embryos for transfer without the need of hyperstimulation, against the possibly negative effects on the children [16].

Data on the third possible comparison, between rFSH and hMG, are scarce. The studies that have been conducted so far found no statistically significant differences with respect to ongoing pregnancy rates [17-19].

The evidence available at this time, comparing the different FSH containing gonadotropin preparations, concerns their usage in IVF. However, almost half of all gonadotropins are used in other settings, such as IUI. Very little data is available comparing the preparations for this indication.

With respect to adverse effects of exogenous FSH administration, no significant differences have been found between products. The main risk associated with the use of FSH containing gonadotropin products is the development of the ovarian hyperstimulation syndrome (OHSS). This is a serious condition characterised by increased vascular permeability and liquid accumulation in the peritoneal, pleural, and pericardial cavities, which occurs in 1-2% of cases [20]. The incidence of OHSS does not differ between products [12,13].

## **PATTERNS OF SUBSTITUTION**

### ***Before 1995***

Since the 1960s two hMG products have been available on the market: Humegon® from Organon, and Pergonal® from Serono. The first change in the market came in 1986 with the introduction of uFSH (Metrodin®, Serono). In 1991, a reference pricing system was introduced in the Netherlands for the reimbursement of prescription drugs through community pharmacies. This means that all pharmaceuticals are clustered into groups with the same therapeutic efficacy. Then a price reference is set as a reimbursement limit in such a way that there is enough opportunity for the insured to receive proper medication without co-payment. uFSH was categorised in the same cluster as hMG with a maximum reimbursement level of €10 per 75 IU.

### ***1995-1996***

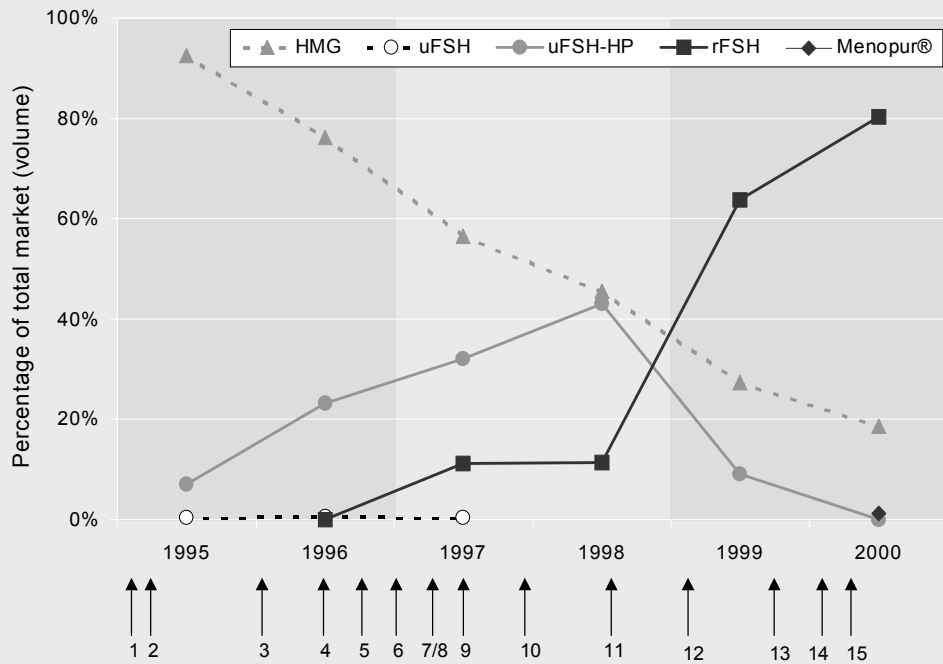
The uFSH-HP preparations were introduced to the Dutch market in February 1995. As can be seen in Figure 1A, uFSH-HP and hMG divided the market between them, leaving only a negligible share for uFSH. While in 1995 hMG products held a more than 90% share of the market volume and uFSH-HP less than 7%, in 1996 uFSH-HP had increased to a 23% market share. Metrodin HP® was by far the largest uFSH-HP provider (>95%); the contribution of Follegon® to the gonadotropins market has been negligible. The question can be raised whether the growth of uFSH-HP at the expense of hMG preparations was supply driven or demand driven. Probably it was both. On the one hand, the meta-analysis presented by Daya et al.[5] in 1995, which concluded that FSH alone was more effective than hMG, may have increased the demand for FSH-only products. Since Serono phased out Metrodin® when Metrodin HP® was introduced, uFSH-HP was the only available pure FSH option. On the other hand, the choice for FSH-only products may also have partly been forced on the market, since there was a shortage of hMG products.

**Table 3** History

| No.  | Date           | Event  |
|------|----------------|--|
| (1)  | February 1995  | Introduction of Follegon <sup>®</sup> and Metrodin HP <sup>®</sup>   |
| (2)  | April 1995     | Presentation of meta-analysis by Daya et al.[5] at conference (publication follows in August 1995)   |
| (3)  | 1995 – 1996    | Shortages of hMG (Pergonal <sup>®</sup> and Humegon <sup>®</sup> ).<br>Delivery of Metrodin HP <sup>®</sup> directly to certain pharmacies below the official price. |
|      | May 1996       | Production of Pergonal <sup>®</sup> has been stopped [11].   |
| (4)  | July 1996      | Metrodin <sup>®</sup> removed from Z-index.  |
| (5)  | September 1996 | Introduction of Gonal-F <sup>®</sup> .   |
| (6)  | January 1997   | Introduction of Puregon <sup>®</sup> .   |
| (7)  | March 1997     | Introduction of Menogon <sup>®</sup> .   |
| (8)  | April 1997     | Start of Puregon <sup>®</sup> restitution action.  |
| (9)  | July 1997      | Meta-analysis Out et al.[10]   |
| (10) | November 1997  | Start of Metrodin HP <sup>®</sup> action: now available at a price equal to the reimbursement level.   |
| (11) | August 1998    | Report by Study Group Recombinant Gonadotropins sent to Health Insurance Fund Council.   |
| (12) | February 1999  | rFSH gets a separate reimbursement cluster: now fully reimbursed.<br>End of Puregon <sup>®</sup> restitution action.<br>End of Metrodin HP <sup>®</sup> action       |
| (13) | September 1999 | Meta-analysis Daya et al.[11]  |
| (14) | February 2000  | Meta-analysis Agrawal et al.[6]  |
| (15) | May 2000       | Metrodin HP <sup>®</sup> removed from Z-index.   |

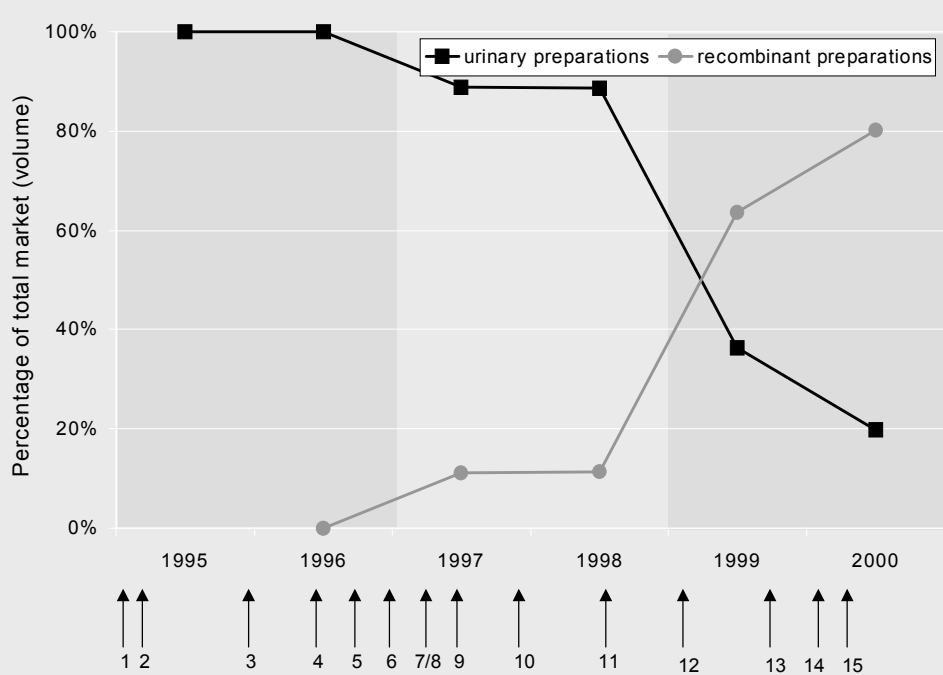
In May 1995, Serono sent a letter to all Dutch gynaecologists explaining the decreased production of Pergonal<sup>®</sup> (capacity problems and a shortage of urine due to the production of Metrodin HP<sup>®</sup>) [21]. One year later, in May 1996, the Newsletter of Freya, the patient federation for fertility problems, reported that the production of Pergonal<sup>®</sup> for the Netherlands had been totally abandoned [22]. Organon experienced difficulties as well, with the production of its hMG product Humegon<sup>®</sup> [23,24]. The shortage of hMG products may have forced doctors and their patients to use uFSH-HP; a worry that was indeed expressed by Freya [22]. Freya was all the more concerned, since uFSH-HP products required a co-payment. Like uFSH, uFSH-HP had been included in the same cluster as hMG with a maximum reimbursement level of €10 per 75 IU. This meant that for Metrodin HP<sup>®</sup> one had to pay a co-payment of €8 per 75 IU ampoule, which gave an average co-payment of €160-240 per cycle (150-225 IU for 10 days) (see Table 4).

**Figure 1a** Diffusion of gonadotropin preparations in the Netherlands



The numbers refer to the events in Table 3

**Figure 1b** Substitution of urinary products by recombinant products



The numbers refer to the events in Table 3



In some selected pharmacies, however, patients were able to purchase the product at a reduced cost, since Serono, the producer of Metrodin HP<sup>®</sup>, made direct deliveries to these pharmacies, thus circumventing the wholesaler's margin. IVF centers were informed to refer their patients specifically to the selected pharmacies. This construction soon had to be abandoned, since it caused a lot of criticism, especially from the Royal Dutch Association for the Advancement of Pharmacy [25-28].

### **1997-1998**

The rFSH products Gonol-F<sup>®</sup> and Puregon<sup>®</sup> were introduced in September 1996 and January 1997 respectively, and in the subsequent 2 years they conquered 11% of the total FSH market. The volume of uFSH-HP continued to increase, and hMG further decreased so that both had a ca. 45% market share in 1998 (see Figure 1A).

The 11% market share of rFSH within 2 years appears relatively modest. There may be two reasons for that. First, the clinical benefits of rFSH were debated. The discussions centered around the clinical trials being industry sponsored or associated, the potency of rFSH preparations (should 50 IU rFSH be regarded as equipotent to 75 IU urinary FSH?), and the quality of the harvested oocytes [29-33]. In any event, it appears that at first the evidence that had to support the superiority of rFSH was convincing neither to the Dutch Health Insurance Fund Council or to the Minister of Health, as they decided to categorise rFSH in the same reimbursement cluster as the urinary preparations, setting its reimbursement level at €10 per 75 IU. This is the second reason to explain the relatively slow uptake of rFSH: the co-payment for rFSH products could amount to €700 per cycle. Organon, the producer of Puregon<sup>®</sup>, started a campaign in which patients could submit the receipt of their co-payment and get a refund of about 75%. At the same time, Serono started a similar campaign, not for its rFSH product Gonol-F<sup>®</sup>, but for Metrodin-HP<sup>®</sup>: temporarily this could be obtained from Serono's distributor by all Dutch pharmacists at a price of €10 per 75 IU (official price was €16) [34].

Another important event was the introduction of a third hMG preparation, Menogon<sup>®</sup>, by a new player in the field, Ferring. While Organon and Serono brought down or even abandoned the production of hMG preparations, either voluntarily or forced by circumstances, the introduction of Menogon<sup>®</sup> made hMG available again. For sure, this has played a significant role in the persistence of hMG as one of the available products in this class.

### **1999-2000**

In March 1998, the Study Group Recombinant Gonadotropins, in which were represented among others the patient federation Freya and the Dutch Association of Gynaecologists, sent a report to the Health Insurance Fund Council entitled 'Therapeutic Value of Recombinant Gonadotropins'.

**Table 4** Product availability

| 1990-1994 |              |          |                 | 1995-1996 |              |            |                 |
|-----------|--------------|----------|-----------------|-----------|--------------|------------|-----------------|
| product   | brand        | supply   | 75 IU price (€) | product   | brand        | supply     | 75 IU price (€) |
| HMG       | Humegon®     | OK       | 10              | hMG       | Humegon®     | shortage   | 10              |
|           | Pergonal®    | OK       | 10              |           | Pergonal®    | shortage   | 10              |
| UFSH      | Metrodin®    | OK       | 15              | uFSH      | Metrodin®    | phased out | 16              |
|           |              |          |                 | uFSH-HP   | Metrodin HP® | OK         | 18              |
|           |              |          |                 |           | Follegon®    | OK         | 16              |
| 1997-1998 |              |          |                 | 1999-2000 |              |            |                 |
| product   | brand        | supply   | 75 IU price (€) | product   | brand        | supply     | 75 IU price (€) |
| hMG       | Humegon®     | shortage | 10              | hMG       | Humegon®     | shortage   | 10              |
|           | Menogon®     | OK       | 10              |           | Menogon®     | OK         | 10              |
| uFSH-HP   | Metrodin HP® | OK       | 16              | uFSH-HP   | Metrodin HP® | phased out | 16              |
|           | Follegon®    | OK       | 22              |           | Follegon®    | OK         | 22/10           |
| rFSH      | Gonal-F®     | OK       | 30              | rFSH      | Gonal-F®     | OK         | 34              |
|           | Puregon®     | OK       | 34              |           | Puregon®     | OK         | 34              |

The Study Group concluded that the recombinant gonadotropins are safer, and that they carry therapeutic and economic benefits, compared to the urinary gonadotropins [35]. The goal was to convince the Health Insurance Fund Council (HIFC) and the Minister of Health to create a separate reimbursement cluster for the rFSH preparations. In an advice to the Minister, the HIFC adopted the increased efficacy of rFSH, but not the economic benefits nor the increased safety profile [36]. Based on this advice, the Minister decided to introduce a separate cluster for rFSH with a reimbursement level of €34 per 75 IU. As a result, from 1 February 1999 onwards, rFSH was fully reimbursed. Both the Puregon® and the Metrodin HP® campaigns of refunding patient's co-payments were stopped immediately by Organon and Serono, respectively.

As a consequence of this development, the volume of rFSH increased explosively to a 64% market share in 1999 (see Figure 1A). The growth levelled off in 2000 (80% volume for rFSH). The large increase of rFSH was mainly at the expense of uFSH-HP, which dropped to 9% volume share in 1999, and 0% in 2000. The market share of hMG continued to decrease to 19%, with Menogon® providing more than 70% of the total hMG market in 2000.

In 1999, the market share of uFSH-HP started to decrease for the first time since 1995. In 2000, Metrodin-HP® even disappeared from the market. An important explanation for this is of course that Metrodin-HP® was the only product for which a co-payment was still required.

It seems that in 2000 the growth of rFSH levelled off, and that the decrease of urinary preparations slowed down (see Figure 1B). While in 1995-1999 the idea ruled that uFSH was probably superior to hMG for use in ovary stimulation for IVF, in 2000 this was questioned again, mainly through the meta-analysis by Agrawal et al.[6] Agrawal argued that some exposure to LH may be beneficial, and indeed her meta-analysis of 11 trials using the long GnRH agonist protocol showed that hMG and uFSH yielded similar results. On the other hand, Daya's analysis [11] pointed in the direction of rFSH being superior to urinary FSH.

### **Current developments**

For each IVF cycle, women need a once daily injection during an average 10 days and in the Netherlands almost all the women administer these themselves. In the period 1995-1999, the products described were marketed as a lyophilised powder (generally 50, 75, 100 or 150 IU) with a separate container of 1 ml solvent. Thus, before injecting themselves, the women first had to dissolve the lyophilised FSH powder in the solvent. Since June 2000, Puregon® has been available as a ready-made solution (Puregon® Solution). This makes its administration easier and, moreover, the volume has been decreased from 1 ml to 0.5 ml. Generally, a smaller volume is associated with less pain upon injection. In addition, Organon has introduced a pen for self-injection, similar to the ones used by diabetics to administer insulin. The Puregon® Pen is to be filled with cartridges of 300 or 600 IU (for multiple injections) and has a dosing mechanism, which can be adjusted in steps of 25 IU. For 50 IU, the volume of injection is only 0.06 ml. The pen can be re-used and costs €23, although many gynaecologists received copies for free distribution among their patients. In April 2000, Organon sent a letter to all Dutch gynaecologists stating that the availability of Humegon® would be terminated on 1 July 2000 [37]. Serono introduced Gonal-F® 600 IU/ml Multidose to the Dutch market in June 2001. This lyophilised powder of 1200 IU (retrieval 1050 IU) has to be dissolved once in the accompanying solvent and can subsequently be used for several days. The injection volume is small. However, the increased convenience for patients of these newly

introduced rFSH products may come at a cost, since the increased amount of rFSH per package (minimum 300 IU for Puregon® Pen and 1050 IU for Gonal-F® Multidose) might lead to more waste.

In July 2000 Ferring introduced a new product: Menopur®. This consists of highly purified (purity >97.5%) urinary FSH 75 IU and LH 75 IU (hMG-HP). It is marketed as a lyophilised powder with a separate container of 1 ml solvent. The price is €23 per 75 IU, which means that a co-payment of €13 is required per ampoule, since the product is clustered with the other, less pure, hMG products. However, Ferring has started a campaign through which patients can receive a complete refund of their co-payments. In 2000, the market share of Menopur® was 1%.

## **DISCUSSION**

Decision-making about (biotechnology) drugs takes place at different levels [38]. On the macro level, politicians, regulators and health insurers have to decide about the licensing and reimbursement of pharmaceuticals. On the intermediate level, decisions are made by specialist organisations, e.g. in developing good practice guidelines, and formulary committees. Ultimately, on the micro level, physicians and patients make choices about individual treatments. Together, all these decisions determine the fate of a biotechnology drug, and its diffusion into society and medical practice. When looking at the diffusion of rFSH, the most crucial decision-making has taken place on the macro level, namely the decisions about its reimbursement. The uptake of rFSH was held back by the fact that a substantial co-payment was required and as soon as this matter was resolved, the switch towards rFSH assumed high proportions. Apparently, gynaecologists and patients (on the meso and micro level) were already in favour of rFSH, but not enough to accept the accompanying co-payment. That is why they brought together the Study Group Recombinant Gonadotropins, which successfully requested the Minister of Health to reconsider a separate reimbursement cluster for rFSH.

In addition, the pharmaceutical companies constitute an important influence in the diffusion process. Regularly, the topic of the influence of the pharmaceutical industry on the medical community is discussed in the medical scientific journals [39-41]. In the case of rFSH, the influence of the FSH producing companies is easy to point out. The fact that the production of hMG and uFSH in the period 1995-1996 remained far behind the needs at that time, benefited the adoption of uFSH-HP. At a later stage, this influence was somewhat constrained by the entry of a third player to the market (Ferring), which marketed hMG as its only gonadotropin product. During the period 1997-1998, both Serono and Organon put together actions to reduce co-payments for patients. By choosing the products for which these actions were installed, they could influence the adoption patterns. Organon chose to focus on rFSH, while Serono put its bet on uFSH-HP.

The first biotech substitutes which were introduced in the 1980s, recombinant insulin and recombinant growth hormone, have never really needed to show superiority compared to the previously used products they were replacing. When recombinant human Growth Hormone (GH) was granted a marketing authorisation in 1985, the previously used pituitary derived products had just been withdrawn from the market due to contamination with the agent causing Creutzfeldt-Jakob disease. As such, recombinant GH automatically gained a 100% market share. Regarding insulin, the debate was not whether recombinant insulin was better than animal insulin, but whether it was not worse. Namely, recombinant insulin was suspected to raise the risk of hypoglycaemia as compared to animal insulin [42-44]. In spite of this discussion, during the 1980s virtually all diabetic patients switched to recombinant insulin and since the early 1990s animal insulin has not even been available anymore in the Netherlands. Again, similar to the rFSH case, the pharmaceutical companies played a major part in this, since they simply withdrew their animal insulin from the market [45]. Reimbursement was less of an issue at that time, since the reference pricing system was not yet in place and recombinant insulin was only a little bit more expensive than animal insulin (<10%).

At the time of the introduction of rFSH, however, the reference pricing system was in place and evidence of clinical superiority was very important. When comparing rFSH to uFSH/uFSH-HP, an absolute increase in pregnancy rates of 3.7% (95% CI 0.5-6.9%) has been demonstrated in a Daya's meta-analysis [11]. The discussion still centers around the question whether this difference is clinically relevant. A 3.7% absolute difference, means that the number of women needed to treat with rFSH instead of uFSH/uFSH-HP in order to gain one additional pregnancy is 27 (95% CI 14-200). The fact that two types of rFSH (the alpha and beta variant) are compared to 2 types of urinary FSH (uFSH and uFSH-HP) further complicates the discussion. Another potential comparison, rFSH versus hMG, initially was not given much attention. Apparently, in the early period after introduction of rFSH, it was commonly assumed that if rFSH could be demonstrated to be superior to uFSH/uFSH-HP, it was also superior to hMG. Given the results of Daya's meta-analysis [5] this seemed logical indeed. However, since: (1) a subsequent meta-analysis [6] pointed in the opposite direction, (2) uFSH is hardly available anymore, and (3) a hMG-HP preparation has been introduced to the market (Menopur®), the question about the comparison between rFSH and hMG (and hMG-HP) has started to become relevant. Overall, the background of several studies using different comparisons and endpoints gives occasion to the fact that the discussion and assessment of the different gonadotropin preparations remains twisty.

That the superiority question is not an easy one to answer is illustrated also by the changeable decisions of the Dutch government. Initially, the Dutch Minister of Health was not convinced of rFSH's superiority and included it in the cluster of the

urinary gonadotropins. A few years later, however, its opinion was altered and a separate reimbursement cluster for rFSH was created. In the meantime a report by the Dutch Health Council had been written, in which it was stated that cryopreservation had become an accepted part of IVF cycles (even though the effects on the resulting 'cryo-children' was unknown and further research on that topic was required). This made it possible for the Minister to accept the efficacy endpoint of cumulative pregnancies, including pregnancies from cryo-cycles. The meta-analyses by Daya [11] and Agrawal [6] were published after the Minister's decision in 1998, and as such the debate on the clinical benefit of rFSH is still ongoing [29-33]. It can be anticipated that further clinical trials and meta-analyses comparing rFSH and hMG (or hMG-HP) will be published in the future. Moreover, the debate about the cost-effectiveness of rFSH will continue. The incremental cost-effectiveness ratio of rFSH compared with uFSH-HP has been estimated at about 12,000 US dollars per additional ongoing pregnancy, assuming an absolute increase in pregnancy rate of 6.4% (including thawed embryos) [46]. When, a 0.5% difference was assumed the estimate was about 70,000 US dollars [46]. In spite of the ongoing debate, the total FSH market has grown from €5.0 million in 1995 to €26.8 million in 2000 (>400% increase), while the total volume increased by <100% in that same period. This can of course be explained by the fact that rFSH is >3 times more expensive per unit than urinary preparations. In 1999, the ovulatory inductive medicines caused the fourth biggest cost increase for pharmaceuticals after gastric acid inhibitors, cholesterol lowering agents and antidepressants [4].

In addition to the data provided to us, this study is based only on published literature, written reports and correspondence filed in the archive of the patient federation Freya. We did not acquire inside information from the parties involved, such as government officials, doctors and the pharmaceutical companies. This of course could constitute a valuable addition, to further deepen the insight in the processes underlying the diffusion patterns that we observed.

In general, the development of recombinant substitutes for already existing compounds was based on several factors, such as potential scarcity of the 'classical' product (future shortages had been forecasted for animal insulin and for plasma derived Factor VIII [47-49]) and fascination with genetic engineering, but also on the assumption that distinct benefits would result from the use of products which were as pure as possible. With respect to pharmaceutical quality, the increased purity and batch-to-batch consistency of the recombinant proteins can be considered a breakthrough. To the pharmaceutical companies it means a more efficient and well-controlled production process. It frees the companies of the complicated logistics of collecting of large amounts of pancreas, pituitary tissue, urine or blood plasma, the supply of which may be uncertain, since it depends on the willingness and cooperation of donors. Moreover, the use of urine as a source for medicines raises

concerns about potential contamination with pathogenic micro-organisms. Plasma derived Factor VIII, for example, has infected many haemophilia patients with HIV and hepatitis C. Especially in the current era of 'prion scare', this may be an important argument in favour of biotech substitutes. On the other hand, urinary derived gonadotropins have been available since the beginning of the 1960s, and so far prion or other infectivity has never been ascribed to them. Notwithstanding the pharmaceutical advantages, significant medical benefits in clinical practice have never been convincingly demonstrated for biotech substitutes, such as recombinant insulin and recombinant Factor VIII, and for rFSH the debate is still ongoing [45,50]. As such, the adagio 'the purer, the better' may be of limited value from the clinical perspective.

Appraising innovations only on their immediate apparent clinical benefits is not a very profound method of technology assessment. Recombinant insulin, as such, did not have relevant clinical benefits over animal insulin [45]. However, it has been an important incentive to continue the development of other valuable biotechnology drugs and vaccines, such as erythropoetin and hepatitis B vaccine. As a rule innovations take place gradually. If the first biotechnology drugs would not have been given a fair chance, we might not have had the knowledge, the experience and the new biotech drugs in development that we have now. Similarly, if recombinant human insulin would not have been given a chance in the 1980s, the short acting insulin analogues, like insulin lispro and insulin aspart, would today probably not be available. The gonadotropin market is also still innovating, with the introduction of ready-made solutions and pens for injection, although these are not necessarily biotech related. Still, these products may represent a considerable step forward to the patients who are using them. In general, the risk of increasing pharmaceutical costs without clear clinical benefits has so be set against the risk of strangling innovations [2]. This, of course is not an easy judgement to make, especially at the beginning of the life-cycle of a new pharmaceutical. Usually, the real advantages and disadvantages of a new medicine become apparent only after it has been used for some time. Therefore, a continuous process of technology assessment is warranted.

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# 10

## Summary and general discussion

## BACKGROUND

Modern biotechnology drugs, such as recombinant human insulin and recombinant human growth hormone, were first developed in the early 1980s. The rapid clinical success of the first recombinant proteins drove large investments and placed high expectations on the young biotechnology industry [1]. Later enthusiasm subsided somewhat, as failures occurred and the number of new biotech introductions did not live up to the high expectations [2,3]. Still, analysts predict that in the long term, about 20-25% of the world drug market will be supplied with products based on genetic engineering methods [4].

Attitudes towards technology vary from great aversion and fear, to technology being seen as a blessing and the most important, if not the only, tool of value in solving problems. This applies to biotechnology as well. Advances in medical research and technology are often the last straw for people suffering from serious disease. However, in the public opinion genetic engineering is also associated with the danger of its usage to eliminate displeasing races and create 'super humans' [5,6]. High tech developments strike the imagination, but at the same time there is a plea for a critical assessment. The continuous increase of the health care costs in the Western countries further adds to the need of careful evaluation of health care technologies [7-9]. However, mixed feelings about this topic exist [10]. On the one hand the need of cost containment is generally acknowledged, on the other hand patients generally expect every effort to be made to improve their health.

In the light of these ambivalent observations, the general aim of this thesis was to explore the broad field of the assessment and the diffusion of biotechnology drugs. Special attention was given to the issue of economic evaluations in health care and to the substitution of already existing compound by biotechnology alternatives.

## MAIN FINDINGS

### *Medical Technology Assessment*

In Chapter 2, we studied the process of assessment and diffusion of biotechnology drugs by studying three cases, i.e. nebacumab, filgrastim and recombinant human growth hormone. The cases were evaluated in a standardised format, concerning safety, efficacy, cost-effectiveness and ethical, legal and social factors.

Many factors that determined the fate of these biotechnology drugs seemed to be similar to those of 'classical' drugs. Uncertainties remained about the effectiveness of the drugs in general practice and about their efficacy in special subgroups or circumstances. Another important area of discussion was the definition and measurement of clinically relevant outcome measures. In the cases studied, intermediate endpoints were often used. The relatively small number of patients was an important limiting factor for clinical programs evaluating efficacy, as only small trials were feasible. We identified the broadening of the range of indications as an

important strategy in certain classes of drugs, which could strongly influence the diffusion of these compounds.

The high costs of many biotechnology drugs attracted extra attention and made the existing issues more pronounced. They were an important driver of the complex adoption processes.

### ***Economic evaluation and abciximab***

In Chapter 3, the attitude of decision-makers towards economic evaluations was studied. Interviews and surveys were conducted with politicians, regulators, hospital pharmacists and physicians in the Netherlands. Generally, the decision-makers had a positive attitude towards economic evaluations. However, most decision-makers did not want to adopt a strict attitude and they stated that decisions should not be based on economic reasoning alone. The actual use of economic evaluation, and knowledge about it, was still limited. Hospital pharmacists and regulators were more fact oriented than physicians and politicians, who also based their judgements on other societal values. The decision-makers preferred to make their own broad comparisons of advantages and disadvantages, and did not base their decisions on a single summary measure only. Our findings were similar to the findings in other European countries.

In Chapter 4, we studied the cost-efficacy of the combined usage of stenting and abciximab in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). The 6 months efficacy data from a large randomised controlled trial (the EPISTENT trial [11]) were combined with Dutch estimates of unit costs. The cost-efficacy ratio that resulted strongly depended on the comparator treatment considered (either stenting or abciximab usage alone) and the composite endpoint chosen (either myocardial infarction-free (MI-free) survival or major adverse cardiac event-free (MACE-free) survival). Compared to abciximab usage alone, the cost-efficacy ratio was €39,000 (95% upper limit (u.l.) €1,400,000) per additional MI-free survivor, and €12,000 (95% u.l. €31,000) per additional MACE-free survivor. Compared to stenting alone, the cost-efficacy ratio was €13,000 (95% u.l. €27,000) per additional MI-free survivor, and €14,000 (95% u.l. €50,000) per additional MACE-free survivor. In the subgroup of diabetic patients more favourable cost-efficacy were found, with uncertainty regions indicating potential costs savings.

In Chapter 5, we used effectiveness data from daily clinical practice to study the costs and effects of stenting plus abciximab as compared to abciximab administration alone. The same estimates of unit costs were applied as in the previous study. It was confirmed that stented patients experienced less major adverse cardiac events than non-stented patients did (6.9% vs. 16.9%, OR= 0.37, p=0.04). Adjustment for

baseline characteristics yielded similar results, although significance subsided. The relative risk reduction of 44% that was found closely resembled the 42% that was found in the EPISTENT trial. The total costs were similar for stented and non-stented patients (€7,844 vs. € 7,904,  $p=0.93$ ).

Chapter 6 described our study of the patterns of abciximab prescribing in Dutch PTCA centres in 1998. All thirteen centres co-operated in the study. The level of abciximab prescribing varied from 2% to 36% of all PTCAs. The criteria for patient selection significantly differed between centres. Together, the size of the budget, participation in clinical trials (investigatorship), size, and type of the institution were highly associated with the level of abciximab prescribing ( $R^2=0.93$ ,  $p<0.001$ ). The more patients doctors had included in clinical trials in the past, the higher was the likelihood that they prescribed abciximab.

### ***Diffusion of biotech substitutes***

Chapter 7 and 8 reported about the introduction of recombinant Factor VIII (rFVIII) as a substitute for plasma derived Factor VIII (pdFVIII). It was found that its diffusion was regulated to a great extent by the Dutch Hemophilia Treaters Society, as they decided upon a gradual introduction of rFVIII. The main reason for this was that switching all Dutch patients to rFVIII would mean the end of the production of Dutch pdFVIII. This was considered not to be a desirable situation, as history had taught that in case of problems with one specific product, it was an advantage to have several producers at one's disposal. In addition, the hemophilia physicians agreed to prescribe rFVIII to all previously untreated patients (PUPs). Both agreements were largely adhered to, as was demonstrated by the results of our postal surveys among both patients and physicians.

Both the patients and the physicians agreed that the physician and not the patient was the most influential in choosing between pdFVIII and rFVIII. Of the responding physicians, only one doctor would choose to use pdFVIII if he would suffer from hemophilia A himself, and 74% would choose to use rFVIII. Overall these physicians prescribed rFVIII to 56% of their patients, however the variation between centers was wide. The physicians indicated that age was the only factor that influenced their decision to prescribe either pdFVIII or rFVIII to a patient. In our study among patients, we found that infection with HIV or hepatitis C, and having family members who use pdFVIII, were negatively associated with switching from pdFVIII to rFVIII. Innovativeness, empowerment, high social economic status, and having family members who use rFVIII were positively associated with switching. This meant that, although the overall pattern of substitution was largely determined by the Dutch Hemophilia Treatment Society, patient preferences did have a modest influence in the diffusion of rFVIII as well.

In Chapter 9, we studied the diffusion of different gonadotropins preparations, including the recombinant Follicle Stimulating Hormone (rFSH) preparations that were introduced since 1996. The diffusion of rFSH was strongly influenced by reimbursement decisions of the Dutch government. In the reference pricing system rFSH was first categorised in the same reimbursement cluster with the human menopausal gonadotropins (hMG) and purified urinary FSH. This meant that a co-payment of up to € 700 per IVF cycle was required for the use of rFSH, and that its market share got stuck at 11% only. A report written by representatives of the Patient Federation for Decreased Fertility and the Dutch Association of Gynaecologists changed the mind of the Minister of Health and she agreed to fully reimburse rFSH from 1 February 1999 onwards. Subsequently, the sales of rFSH increased exponentially to an 80% market share in 2000. As rFSH was three times as expensive as the former gonadotropin preparations, total FSH expenditures grew from €5.0 million in 1995, to €26.8 million in 2000. In addition to the government, the pharmaceutical companies themselves also influenced the diffusion of the different gonadotropin preparations. They refunded co-payments for some products and not for others. Moreover, product shortages of one product benefited the adoption of another. The debate of the relative therapeutic value of rFSH over other gonadotropins has not been settled yet.

## **INNOVATION IN MEDICAL TECHNOLOGY**

Efficacy and safety are the basic starting points in evaluating the overall utility of new medicines. Neither the need for a new drug, nor its appropriate use in medical care can be established without reliable and valid information on efficacy and safety. However, studies on the development and diffusion of innovations have shown that safety and efficacy are not the only factors that determine the fate of a new compound. Other characteristics of an innovation, such as the degree to which the results of the innovation are visible (observability) or the degree to which the innovation is perceived as consistent with the existing ideas and past experiences (compatibility), influence its rate of adoption as well [12]. In addition to characteristics of the innovation, there are other factors that affect its adoption process as well. Rogers mentions, for example, the type of innovation decision (optional, collective or authority), the communication channels, the nature of the social system and the extent of the promotion efforts [12]. The evolutionary perspective on innovation and economics is correlated to the concept of adaptation to local environments. It assumes that the parties involved can never be 'perfectly informed' and that they are bound to rules, norms and institutions. In this perspective, decision making is, at best, locally good rather than globally optimal [13].

Similarly, in the concept of ‘the social construction of technology’ an innovation becomes a success not necessarily because of the intrinsic nature of the technology but as a result of social interplay and power politics [14]. Often there is an initial period of competing technical alternatives and uncertainty, followed by a period in which one alternative becomes dominant both in the market and in the way scientists think about the technology.

In Chapter 2 we analysed the cases of three biotechnology drugs in a standardised way covering: 1) safety, 2) efficacy/effectiveness, 3) economic evaluation, and 4) ethical, legal and social factors [15]. These are the principle facts with which medical technology assessment (MTA) is concerned (Figure 1). However, in the light of the aforementioned theories on the process of innovation, it was not surprising that decision-makers mentioned not only these factors, but also politics as an important factor in the assessment of health care technologies. As depicted in Figure 2, there are different stakeholders that together determine the fate of a biotechnology drug. Although they will all consider the same facts in the MTA matrix, they inevitably are influenced by their own political motives, beliefs and values. All stakeholders are influenced by values as they act from their own biasing embodiment. Even researchers, who like to portray themselves as mere observers of reality (‘modest witnesses’), inevitably are influenced by their own beliefs and interests. Randomised controlled clinical trials are widely considered to be the pathway to objectivity in medical research. However, McCormack and Greenhalgh [16] showed that even the report of their results might be subject to biases. Prior expectations, enthusiasm for a positive results, the political need for regular high impact medical breakthroughs, and the tendency of clinicians to overestimate the benefits and underestimate the harms of drug treatment, were mentioned as important biases influencing researchers, authors and editors. The well-known publication bias, i.e. the fact that negative results tend not to be published, of course strongly relates to this issue.

The next paragraphs discuss the different stakeholders and the critical issues that we identified in our studies.

### **Stakeholders**

Patients, physicians, pharmacists, researchers, pharmaceutical companies, health care insurers, government, the media, and the general public are all stakeholders in the assessment and diffusion of biotechnology drugs (Figure 2).

On the macro level, government authorities influence the diffusion of biotechnology drugs as they set the rules for the health care systems in different countries. On a lower level, they are influential through their decisions about the approval and reimbursement of drugs. The American Food and Drug Administration (FDA), for example, sped up the approval of rhGH because of the Creutzfeldt-Jakob crisis [13].



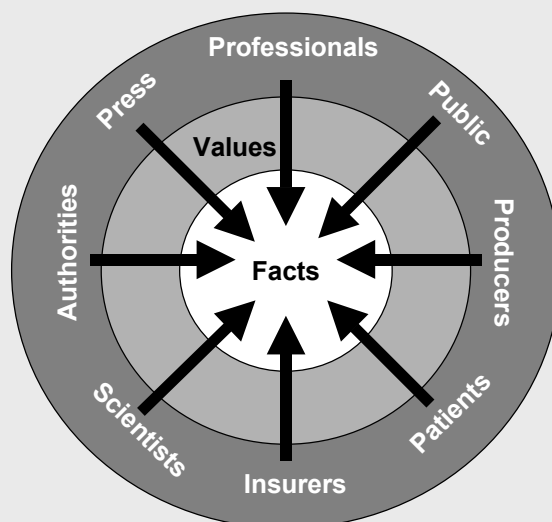
**Figure 1** MTA matrix: principal facts in Medical Technology Assessment [15]

| Safety | Efficacy/<br>Effectiveness | Cost/<br>Cost-effectiveness | Ethical /legal/<br>social factors |
|--------|----------------------------|-----------------------------|-----------------------------------|
|        |                            |                             |                                   |

Due to contamination with the prion causing Creutzfeldt-Jakob disease, pituitary human growth hormone (pit-hGH) had already been withdrawn from the market when the first rhGH product filed for approval with the FDA. Most children took pit-hGH for dwarfism and could forego treatment for a maximum of 6 months without jeopardising their final height. Remarkably, the FDA approved rhGH almost exactly six months after the withdrawal of pit-hGH. The approval took 23 months, which was about half of the normal approval time at that time [13].

The case of the recombinant follitropins (rFSH) clearly demonstrated both the impact of the pharmaceutical industry and of reimbursement decisions. With the current trend towards ‘regulated competition’, reimbursement decisions will be made more and more by health care insurers instead of by governments. As such, health care insurers will become important stakeholders as well. The influence of the pharmaceutical companies has also been described for the case of recombinant human insulin. Recombinant human insulin was introduced in 1982, and by the end of the 1980s virtually all diabetic patients had switched from animal to recombinant insulin [17,18]. Since the early 1990s animal derived insulin is not commercially available anymore in The Netherlands. The pharmaceutical companies played a major part in bringing about this switch. While the discussion on the equivalence of recombinant human insulin and porcine insulin was still ongoing, the leading European manufacturer already announced the withdrawal of the latter human insulin. This was effected within a few weeks in some countries and over six months in the United Kingdom [17]. As such, pharmaceutical companies can influence the diffusion of a biotechnology drug not only through direct promotion efforts, but also through their manufacturing choices and pricing strategies. This influence is greatest, of course, when one and the same company markets two competing drugs. As such, biotech substitutions are a particular example.

As health care professionals, most notably physicians, can be considered as ‘the customers’ for all prescription drugs (on behalf of their patients), their influence on the diffusion of biotechnology drugs hardly needs any explanation.

**Figure 2** The different stakeholders look at the facts through their own values

Notwithstanding the current development towards patient empowerment, the Dutch Hemophilia Treatment Society successfully implemented a policy to restrict the use of recombinant Factor VIII (rFVIII). Interferon-alfa-2a for the adjuvant treatment of melanoma presents another example. Shortly after the approval of this compound by the registration authorities, the Dutch Melanoma Working Group, a multi-disciplinary group of melanoma treating physicians, stated that in their opinion there is no place for interferon-alfa in the treatment of melanoma [19]. The case of rFSH showed the opposite: in this case gynaecologists and patients stood up together for the reimbursement of rFSH. As such, physicians strongly influence the position of other stakeholders. It is very unlikely that the patient federation alone could have achieved the change in reimbursement of rFSH, if the professionals had not supported them. The media and the public opinion constitute another example. The variation in the use of taxoids in Dutch hospitals has received broad media coverage in the Netherlands. This has resulted in a special reimbursement settlement for these products. The large variation in the use of abciximab, however, has gone largely unnoticed. One of the reasons for this, can be the opinion of the professionals. They will only seek publicity when they are strongly convinced of the drug's benefits, and of the need for additional funding.

In conclusion, the influence of the different stakeholders illustrates that innovation in drug therapy requires more than just a new 'technique' or compound. The environment is just as important in the innovation process. For example, the assembly-conveyer would have been unconceivable without the social, financial and

economical innovations that took place during the Industrial Revolution [14]. Similarly, scientific advances in biotechnology and life sciences can not be considered separately from other developments, such as the rise of information technology and the reorganisation of health care systems. In this regard, Smits has underlined the importance of ‘co-evolution’ of scientific, technological and societal systems [20]. Innovation in biotechnology and genomics represents a case par excellence where the need for ‘co-evolution’ is pertinent. Unmet medical needs, orphan diseases and other public health interests require constructive strategies to cope with the fact-value gap.

### ***Critical issues***

The studies in this thesis revealed several issues that are critical in the assessment and diffusion of biotechnology drugs, and that are vulnerable to personal values. They are discussed below.

### ***Economic evaluation***

From the interviews with the decision-makers in Chapter 3 it was concluded that the attitudes towards cost-effectiveness as a criterion varied, and that the actual use of economic evaluations in decision-making processes was still limited. This was confirmed by the studies on Factor VIII, the recombinant follitropins and abciximab. In all three cases, cost-effectiveness did not seem to be of strong influence on the diffusion patterns. In case of recombinant Factor VIII this might be explained by the fact that it is ‘only’ about 10% more expensive than plasma derived Factor VIII. The recombinant follitropins, however, are three times as expensive as the urinary gonadotropins. Statements about the cost-effectiveness of rFSH as compared to uFSH are surrounded by large uncertainties, as the debate about the clinical benefits is still ongoing. Cost-effectiveness played no part at all in the reimbursement decision, which was a strong determinant of the diffusion of rFSH.

With regard to abciximab, it was also clear that cost-effectiveness was not an important factor in the decision-making process. The use of abciximab causes an initial increase in hospital costs, while subsequent savings may not become apparent to the hospital management, since the total number of myocardial infarctions or revascularisation will probably not decrease for various reasons such as existing waiting lists for interventions. Other factors, such as budget and investigatorship were identified as important predictors of the level of abciximab usage within each hospital.

While there is still debate about the cost-effectiveness criterion, all stakeholders agree that safety and efficacy/effectiveness are the basic facts on which the assessment of pharmaceuticals is based.

### *Risk assessment*

This issue is best illustrated by comparing the substitution patterns of three biotech substitutes: rhGH, rFVIII, and rFSH (see Figure 3).

The switch from pit-hGH to rhGH was the quickest switch possible. Because of the history of Creutzfeldt-Jakob disease through the use of pit-hGH, rhGH immediately captured a 100% market share. Plasma derived Factor VIII (pdFVIII) caused many people to be infected with HIV or hepatitis C. Surprisingly this did not speed up the diffusion of rFVIII. On the contrary, the diffusion of rFVIII has followed a very slow and gradual course. The big difference was that one was not able to safeguard pit-hGH from infectious prions, while in 1995 the viral safety of pdFVIII could to a large extent be guaranteed. However, in some countries, all patients were switched from pdFVIII to rFVIII in response to the emergence of Creutzfeldt-Jakob disease as a potential sequela of the Bovine Spongiform Encephalopathy (BSE) epidemic, although transmission through clotting factors has never been documented actually. The issue of infectivity was only a minor theme in the diffusion of rFSH, as transmission of infectious agents had never been documented for urinary gonadotropins. Still, advocates of rFSH sometimes use the biological safety of rFSH as an argument. Fact is, that rFSH did manage to capture a more than 80% market share, while the relative therapeutic value of rFSH over other gonadotropins is still debated.

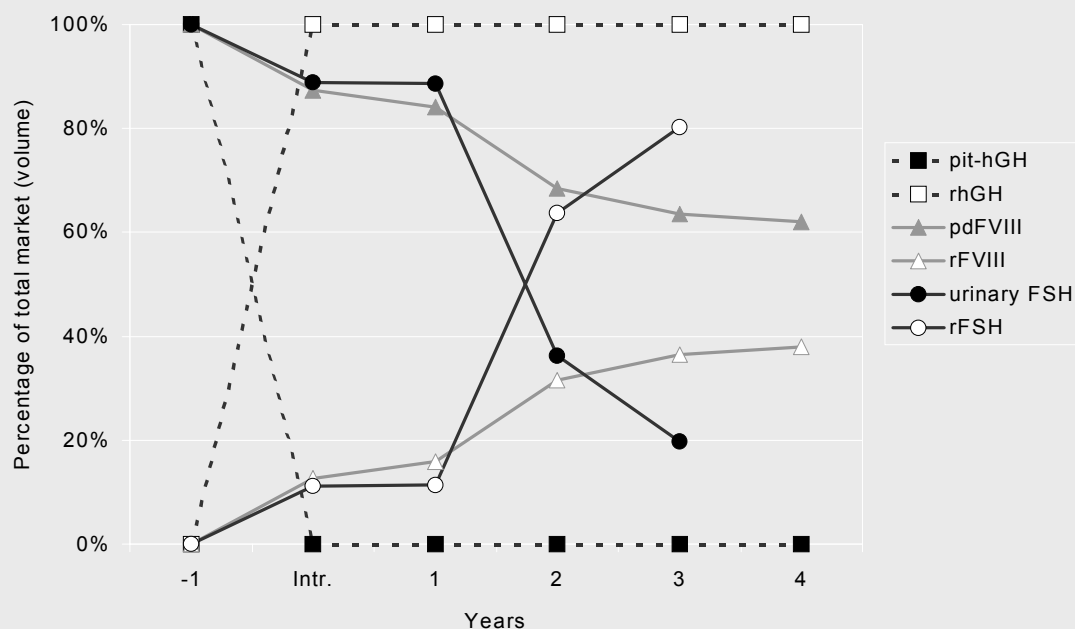
Safety is a relative concept: no drug is ever completely safe. Safety represents a value judgement of the acceptability of risk. The fact that many people are afraid to travel by aeroplane, which statistically is the safest way to travel, illustrates that our attitude towards risk is not purely fact based.

### *Broadening of indications*

Broadening of indications was found in several cases described in this thesis: filgrastim, growth hormone, abciximab (being used and investigated aside from PTCA, in unstable angina) and the gonadotropins (first ovarian stimulation, then also in-vitro fertilisation). It needs no explanation that this issue particularly attracts the attention of decision-makers that have to pay for the products involved. Once a product is included in the reimbursement system, in the Netherlands it is reimbursed for all registered indications. Only in exceptional cases the reimbursement of a drug is restricted to specific conditions ('List 2' of the 'Regulation on Pharmaceutical Care'). In general, the payers hardly have any means to control the use of a pharmaceutical, once it has been approved for reimbursement.

Broadening of indications can be expected for compounds that influence complex regulating systems within the body, such as the immune system. These compounds are likely to be useful in a range of diseases.

**Figure 3** Substitution patterns of growth hormone, Factor VIII and follicle stimulating hormone



*Intr.* = introduction, *pit-hGH* = pituitary human growth hormone, *rhGH* = recombinant human growth hormone, *pdFVIII* = plasma derived Factor VIII, *rFVIII* = recombinant Factor VIII, *Urinary FSH* = urinary Follicle Stimulating Hormone, *rFSH* = recombinant Follicle Stimulating Hormone

The recently introduced infliximab (Remicade®), which is used for the treatment of both rheumatoid arthritis and Crohn's disease, and the interferons, which are used for various oncologic indications and in hepatitis treatment, represent good examples. Many biotechnology drugs, indeed interfere with such complex, comprehensive physiological systems, and are vulnerable to indication dynamics.

### *Generalisability and subgroups*

The issue of the external validity or generalisability of clinical trial results has often been discussed [21-23]. Recently Padkin et al. [24] called it one of the key methodological challenges for achieving a more scientific basis for health care. Closely related to this issue is the identification of subgroups of patients for whom the drug might be (most) beneficial or cost-effective. Patient-characteristics, severity of disease, comorbidity, and compliance are all determinants of the outcome of drug exposure [25]. Often in a clinical trial population only a selection of the distribution of determinants in the normal patient population is represented [25,26]. The

variation in the determinants is kept to a minimum in a clinical trial, in order to be able to reach sufficient statistical power. As a result, the effectiveness of a drug in general practice might be different from the efficacy demonstrated in a randomised controlled trial. One often proposed solution is the conduct of 'everyday practice trials' including a broad range of patients. This, however, goes against the other issue, namely the definition of subgroups in which the treatment is especially beneficial. Even within the current 'homogeneous clinical trials' there is heterogeneity. In the cases of filgrastim, growth hormone and abciximab we found ample debates about this. The topic, of course, closely relates to the question of cost-effectiveness and cost containment. Sometimes a fine-tuning of indications to start treatment occurs within professional groups, e.g. the national consensus on the treatment of hypercholesterolemia [27]. However, these guidelines are not binding to the professionals. In cases of preventive care where the benefit gradually increases over subgroups, the issue of broadening of indications is very pronounced.

As we saw in Chapter 6, budgetary constraints urged cardiologists to engage in the question in which patients abciximab administration is most beneficial. Answers to this question varied, as there were only limited scientific data available. Full information on all imaginable subgroups, however, is unobtainable. Kübler [28] figured out, for example, that it would take more than 450 trials to study all possible treatment strategies in the postinfarction period.

### *Outcome measures*

The definition of clinically relevant outcome measures was another methodological issue identified. The paradigm is to use final endpoints, as history has proven that an improvement of intermediate endpoints does not always result in the expected improvement of the final endpoint [29]. Theoretically, survival adjusted for quality of life would embody the ideal endpoint to be considered (apart from the problems associated with measuring quality of life). As we saw in the cases of growth hormone, filgrastim and abciximab, this information often is not available. As such, interpreting the available evidence remains a matter of judgement and of cost-effectiveness considerations. In case of abciximab for example, some might consider the prevention of myocardial infarctions a clinically relevant goal in itself, others might accept it as a predictor of decreased mortality, and yet others are only satisfied with data on increased survival.

## **FINAL CONSIDERATIONS**

Although many factors that determine the fate of a biotechnology are similar to those of 'classical' drugs, there is at least one phenomenon that is very specific to biotechnology drugs, i.e. the phenomenon of biotechnology substitutions. However, as most compounds that can be replaced have already been replaced by now, this will not be a big issue in the future.

Future biotech drugs will probably often be new compounds that affect comprehensive regulatory systems in the body. As such, broadening of the range of indications is likely. Scientific assessment will rarely provide clear 'yes/no' answers. Seldom will a new biotechnology drug be found to be either worthless or a panacea. Instead the question is usually one far more difficult to answer: 'Who should receive the intervention and under what circumstances?'

Of course, we need data on safety, efficacy and cost-effectiveness to decide about this. However, more data does not necessarily lead to better decisions. The paradigm of statistical significance if  $p < 0.05$ , is an arbitrary one. As such, further research on the medical benefits of an intervention is not necessarily cost-effective. Attention should be paid as well to the mechanisms and incentives that underlie the decision-making processes.

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## SAMENVATTING

In het algemeen varieert de houding ten aanzien van technologische innovatie in onze samenleving van een omarming van technologie als de oplossing voor alle problemen enerzijds, tot grote aversie en angst anderzijds. Deze ambivalente houding bestaat ook ten aanzien van biotechnologie. Het succes van de eerste biotechnologische geneesmiddelen wekte hoge verwachtingen en vormde een stimulans voor de jonge biotech industrie. Het eerste biotechnologische geneesmiddel, recombinant insuline (1982), heeft inmiddels de runder- en varkensinsuline volledig vervangen. Ook het tweede biotech geneesmiddel betrof een alternatief voor een reeds bestaand product: recombinant groeihormoon (1985) nam vrijwel direct de plaats in van hypofysair groeihormoon.

Naast dergelijk substituties zijn er in de afgelopen 20 jaar ook diverse biotechnologische geneesmiddelen geïntroduceerd met een geheel nieuw werkzaam bestanddeel. Filgrastim (Neupogen®), bijvoorbeeld, stimuleert de productie en afgifte van neutrofiële granulocyten door het beenmerg, en kan onder andere worden toegepast ter preventie van febrile neutropenie bij chemotherapie en beenmergtransplantatie. Een ander voorbeeld is abciximab (ReoPro®), een bloedplaatjesaggregatieremmer, waardoor de kans op complicaties tijdens en na een dotterprocedure vermindert.

Uiteraard is een kritische evaluatie van nieuwe geneesmiddelen noodzakelijk. Deze noodzaak wordt nog versterkt door de stijgende kosten voor de gezondheidszorg. Echter, ook op dit gebied treft men een dualistische houding aan. Enerzijds zijn de meeste partijen overtuigd van de noodzaak van kostenbeheersing, anderzijds verwachten patiënten dat veel, zo niet alles in het werk wordt gesteld om hun gezondheid te verbeteren. Aangezien biotechnologische geneesmiddelen vaak dure geneesmiddelen zijn die worden toegepast bij ernstige, levensbedreigende ziektes, kan dit tot spanningen leiden.

Het proces waarin een nieuw geneesmiddel zijn weg vindt in de medische praktijk wordt 'diffusie' genoemd. In dit proefschrift is aandacht besteed aan de beoordeling en de diffusie van biotechnologische geneesmiddelen. Hierbij is met name aandacht geschonken aan economische evaluaties en aan het fenomeen dat sommige biotechnologische geneesmiddelen als alternatief dienden voor vergelijkbare, reeds bestaande middelen die werden gewonnen uit biologisch materiaal.

In hoofdstuk 2 van dit proefschrift werden de wetenschappelijke discussies rondom drie biotechnologische geneesmiddelen bestudeerd met betrekking tot: 1) veiligheid, 2) werkzaamheid en effectiviteit, 3) doelmatigheid en 4) sociaal, ethische en juridische factoren. De drie casussen waren nebacumab, filgrastim and recombinant groeihormoon.

## Samenvatting

Veel factoren die het lot van een biotechnologisch geneesmiddel bepaalden waren hetzelfde als bij 'gewone' geneesmiddelen. Vaak bestond er onzekerheid over de effectiviteit van het geneesmiddel in de dagelijkse praktijk en over de werkzaamheid in bepaalde subgroepen. Een belangrijk punt van discussie was de definitie en de bepaling van klinisch relevante uitkomstmaten. In de bestudeerde casussen werden vaak intermediaire ('surrogaat') eindpunten gebruikt. Een belangrijke limiterende factor voor klinische evaluatie was het relatief kleine aantal patiënten. Hierdoor waren slechts studies van een beperkte omvang mogelijk. Bij bepaalde groepen geneesmiddelen werd indicatie-uitbreiding geïdentificeerd als een belangrijke strategie, die de diffusie van de betreffende middelen sterk beïnvloedde. De hoge prijzen van veel biotech geneesmiddelen trokken aandacht en maakten dat de bestaande discussiepunten als het ware werden uitvergroot. Kosten waren een belangrijke aanjager van het complexe adoptie proces.

In hoofdstuk 3 zijn Nederlandse besluitvormers (artsen, ziekenhuisapothekers, beleidsmakers en politici) geïnterviewd over dit onderwerp. In het algemeen stonden zij positief tegenover het idee dat de kosten en de baten van geneesmiddelen met elkaar in verband worden gebracht, teneinde het beschikbare geld in de gezondheidszorg zo doelmatig mogelijk in te zetten. Echter, de kennis van de besluitvormers over de methodologie van economische evaluatie studies was beperkt en op het moment van de studie (1998/1999) wogen zij informatie over de kosten-effectiviteit van een geneesmiddel nauwelijks mee in hun beslissingen. Ziekenhuisapothekers en beleidsmakers waren meer gericht op de 'harde feiten' dan artsen en politici, die ook meer 'zachte' opinies en gevoelens in hun overwegingen meenamen. De besluitvormers gaven aan dat zij hun eigen afweging van voor- en nadelen wilden maken, en hun oordeel niet wilden baseren op een enkel getal waarin alles wordt samengevat. Zij gaven dan ook aan, met uitzondering van de ziekenhuisapothekers, weinig te zien in het strikt hanteren van een vast afkappunt voor kosten-effectiviteit.

In hoofdstuk 4 werd de kosten-effectiviteit berekend van de gecombineerde toepassing van abciximab en stents bij patiënten die een dotterprocedure ondergingen. De patiënten uitkomsten na 6 maanden van een grote gerandomiseerde studie (de EPISTENT studie) werden gecombineerd met Nederlandse kostprijzen. De daaruit voortvloeiende kosten-effectiviteit ratio was sterk afhankelijk van de gekozen uitgangsbepaling (ofwel alleen stents, ofwel alleen abciximab) en van de gekozen uitkomstmaat (ofwel myocardiinfarct-vrije [MI-vrije] overleving, ofwel ernstige cardiale complicaties-vrije ['major adverse cardiac event'-vrije = MACE-vrije overleving]). Vergeleken met uitsluitend abciximab toediening, was de kosten-effectiviteit ratio €39.000 (95% bovenlimiet [b.l.] €1.400.000) per additionele

MI-vrije overlevende, en €12.000 (95% b.l. €31.000) per additionele MACE-vrije overlevende. Vergeleken met alleen stenten, was de kosten-effectiviteit ratio €13.000 (95% b.l. €27.000) per additionele MI-vrije overlevende, en €14.000 (95% b.l. €50.000) per additionele MACE-vrije overlevende. In de subgroep van diabetes patiënten werden gunstigere kosten-effectiviteit ratios gevonden, met betrouwbaarheids intervallen wijzend op mogelijke kostenbesparingen.

In hoofdstuk 5 werden klinische data uit de dagelijkse praktijk gebruikt om de kosten en effecten van gecombineerd abciximab en stent gebruik te vergelijken met alleen abciximab toediening. Dezelfde kostprijzen werden gebruikt als beschreven in hoofdstuk 4. Het werd bevestigd dat gestente patiënten minder ernstige cardiale complicaties ervaren dan niet-gestente patiënten (6,9 % versus 16,9 %, OR= 0,37, p=0,04). Na correctie voor uitgangskarakteristieken bleven de resultaten hetzelfde, alleen verdween de statistische significantie. De gevonden relatieve risico reductie was 44% en kwam sterk overeen met de 42% die werd gevonden in de EPISTENT studie. De totale kosten waren gelijk voor gestente en niet-gestente patiënten (€7.844 vs. €7.904, p=0,93).

Hoofdstuk 6 beschrijft het patroon van abciximab gebruik door Nederlandse dottercentra in 1998. Alle 13 dottercentra deden mee aan deze studie. Het percentage van de dotterprocedures waarbij abciximab werd toegepast varieerde per centrum van 2% tot 36%. De criteria die werden gebruikt om te beslissen of een patiënt in aanmerking kwam voor abciximab toediening verschilden sterk tussen de centra. In multivariate regressie analyse waren vier factoren sterk geassocieerd met de mate van gebruik van abciximab: het beschikbare budget, participatie in onderzoeken met abciximab in het verleden, en grootte en karakter (academisch/niet-academisch) van het ziekenhuis ( $R^2=0,93$ ,  $p<0,001$ ). Hoe meer patiënten in het verleden waren geïnccludeerd in klinisch onderzoek met abciximab, hoe meer het middel in het centrum werd gebruikt.

Hoofdstuk 7 en 8 handelen over de introductie van recombinant Factor VIII (rFVIII) als een alternatief voor uit plasma gewonnen Factor VIII (pFVIII) voor de behandeling van hemofilie A. We vonden dat het diffusiepatroon voor een groot deel werd bepaald door de Nederlandse Vereniging van Hemofilie Behandelaren, die had besloten tot een geleidelijk introductie van rFVIII. Het belangrijkste argumenten voor dit besluit was dat een radicale switch van pFVIII naar rFVIII het einde zou betekenen van de productie van pFVIII door Sanquin ('de Nederlandse Bloedbank'). Dit werd niet wenselijk geacht aangezien het verleden had geleerd dat het een voordeel is om met verschillende producenten te werken voor het geval dat zich problemen voordoen. De hemofiliebehandelaren kwamen tevens overeen dat

## *Samenvatting*

voorheen onbehandelde patiënten bij voorkeur zouden worden behandeld met rFVIII. Onze enquêtes onder patiënten met hemofilie en hemofiliebehandelaren wezen uit dat beide afspraken grotendeels nageleefd zijn.

Zowel artsen als patiënten gaven aan dat de arts en niet de patiënt de meeste invloed heeft op de keuze voor een bepaald type FVIII product. Slechts 1 van de participerende artsen zou kiezen voor pFVIII als hij zelf ernstige hemofilie zou hebben. In totaal schreven de artsen pFVIII voor aan 56% van hun patiënten. De variatie in dit percentage per arts was groot. De artsen gaven aan dat leeftijd de enige factor was die een rol speelde bij de productkeuze voor een bepaalde patiënt.

In onze studie onder patiënten met hemofilie vonden we dat infectie met HIV, infectie met hepatitis C, en het feit dat iemand familieleden had die pFVIII gebruikten, negatief gecorreleerd waren met het overstappen van pFVIII naar rFVIII. Dit betekent dat, ondanks dat het totale substitutiepatroon grotendeels werd bepaald door de Nederlandse Vereniging van Hemofilie Behandelaren, patiëntenvoorkeuren toch ook een bescheiden rol spelen in de diffusie van rFVIII.

In hoofdstuk 9 werd de diffusie van de verschillende gonadotrofinen preparaten geëvalueerd, met inbegrip van de in 1996 geïntroduceerde recombinant Follikel Stimulerend Hormoon (rFSH) preparaten. De diffusie van rFSH is sterk beïnvloed door de overheidsbesluiten over het al dan niet opnemen van rFSH in het verzekeringspakket. Aanvankelijk werd rFSH ingedeeld in het Geneesmiddel Vergoedings Systeem in hetzelfde cluster als menopauzegonadotrofine (hMG) en urofollitropine. Dit leidde tot bijbetaling tot €700 per IVF cyclus voor rFSH, en het marktaandeel bleef dan ook steken op 11%. Een rapport geschreven door vertegenwoordigers van de Patiëntenvereniging voor Vruchtbaarheidsproblematiek en de Nederlandse Vereniging voor Obstetrie en Gynaecologie deed de overheid eind jaren negentig van gedachte veranderen. Besloten werd dat rFSH vanaf 1 februari 1999 toch volledig zou worden vergoed. Direct begon de verkoop van rFSH exponentieel te stijgen en had rFSH in 2000 een marktaandeel van 80%. Omdat rFSH drie keer zo duur was als de 'oude' gonadotrofinen preparaten, stegen de totale kosten van het gebruik van gonadotrofinen van €5,0 miljoen in 1995 naar €26,8 miljoen in 2000. Naast de overheid hadden ook de fabrikanten zelf invloed op de diffusie van de verschillende gonadotrofinen preparaten. Zij stelden terugbetalingsregelingen in voor bepaalde producten, en niet voor andere. Bovendien profiteerde sommige producten van de leveringsproblemen van andere producten. Ondertussen is het debat over de relatieve therapeutische waarde van rFSH ten opzichte van de anderen gonadotrofinen nog steeds gaande.

De casussen in dit proefschrift laten zien dat de 'menselijke' factor van groot belang is bij de beoordeling en de diffusie van biotechnologische geneesmiddelen.

Wetenschappelijke onderzoeken leveren geen dichotome antwoorden op. De manier waarop de verschillende belanghebbenden wetenschappelijke gegevens ('facts') interpreteren wordt beïnvloed door hun persoonlijk overtuiging, positie, belang en achtergrond ('values'). Zo is er vaak discussie over de externe validiteit van klinische studies en over de werkzaamheid van het geneesmiddel in specifieke subgroepen. Een ander discussiepunt is de definitie van een klinisch relevante uitkomstmaat.

De resultaten van dit onderzoek leveren een verbreding op van de kennis van de beoordeling en diffusie van biotechnologische geneesmiddelen. Bijna nooit zal een nieuw geneesmiddel in alle opzichten waardeloos zijn of in alle opzichten een aanwinst. De vraag die overblijft is veel complexer van aard, namelijk: "Wie moeten in aanmerking komen voor dit middel en onder welke condities?". Om deze besluitvorming te ondersteunen zijn niet alleen klinische data nodig, maar is tevens inzicht vereist in de mechanismen die ten grondslag liggen aan de diffusie-processen. De resultaten van dit onderzoek leveren daartoe een bijdrage.

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Jeannette Zwart-van Rijkom,  
februari 2002



## **CURRICULUM VITAE**

Jeannette Zwart-van Rijkom was born on 6 July 1972 in Utrecht, the Netherlands. After finishing secondary school at the Stedelijk Gymnasium in 's-Hertogenbosch in 1990, she started her pharmacy study at Utrecht University. She obtained the Master's degree 'cum laude' in 1995 and the pharmacist's degree in 1997. From January 1998 until December 2001 she worked on the studies described in this thesis at the Department of Pharmacoepidemiologie and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences. In June 2000 she obtained a Master of Science in Health Services Research at the Netherlands Institute for Health Sciences. As of November 2001, she is working in a hospital pharmacy.