Modelling the Cost-Effectiveness of Delaying End-Stage Renal Disease

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Key Words
Cost-effectiveness · Early assessment · State-transition model · End-stage renal disease · Chronic kidney disease

Abstract
Background: As the incidence of end-stage renal disease (ESRD) is on the rise, new therapies are being developed for delaying ESRD. This study is aimed at constructing a generic model for estimating the cost-effectiveness of delaying ESRD in 7 European countries: the Netherlands, United Kingdom, Germany, Italy, Spain, Finland and Hungary. The use of this model is illustrated by assessing 2 fictitious, but realistic therapy options.

Methods: Quality-adjusted life years (QALYs) and societal costs were estimated using a state-transition model. Age-dependent survival after renal replacement therapy was estimated using data from the Dutch Renal Registry. Healthcare costs and utilities were obtained from published reports. Country-specific differences regarding access to transplantation and value of productivity were factored.

Results: A 1-year delay of ESRD rendered an estimated gain of 0.6 QALYs and 0.3 years in productivity. Access to transplantation had a minimal impact, whereas savings on productivity had a significant impact. For a 1-year delay free of charge, societal savings would range from €8,000 in the United Kingdom to €17,000 in Germany. Applying thresholds of €20,000–€40,000 per QALY gained, one-time cell-based therapy would be economically acceptable if it delayed ESRD by 0.2–0.5 years. It would be cost saving for a delay in excess of 0.5 years. Continuous use of medication is unlikely to be cost-effective for prices higher than €30,000 per year.

Conclusion: This study provides evidence for the economic potential of new therapies delaying ESRD. The constructed model provides users with information about the market success rates of treatment options at an early stage.

Introduction
The worldwide impact of chronic kidney disease (CKD) is high. Following the growing prevalence of diabetes around the world, the incidence of CKD and end-stage renal disease (ESRD) is increasing [1]. In Europe, CKD affects approximately 8% of the population. To cope with the increase in CKD and ESRD incidences, governments spend a considerable part of their healthcare budget on expensive renal replacement therapy (RRT) [2]. In addition, the costs for patients, family and society as a whole
are considerable, due to the impact on the quality of life, ability to work, life expectancy and the invasive character of RRT [3]. Currently, no treatment options are available for restoring the kidney function in patients with CKD. Conventional therapy includes basic pharmacological and life style interventions, which aims at delaying and reducing further damage [1]. New treatment methodologies for delaying ESRD, including, for example, cell-based therapy and biological agents are under development.

Traditionally, renal treatment has been one of the first to undergo economic assessment. The most quoted threshold for cost-effectiveness in healthcare is $50,000 per quality-adjusted life year (QALY), which implies that $50,000 is considered a reasonable price for one additional healthy year. This threshold was derived from the cost-effectiveness ratio calculated for using dialysis in patients with chronic renal failure. If $50,000 per QALY is acceptable for dialysis, then other interventions with similar or better cost-effectiveness could likewise be considered acceptable [4].

In this paper, a model for assessing the cost-effectiveness of new treatments that delay ESRD is presented. This model allows assessing the economic potential of new therapies in an early phase of their development, based on preliminary estimates of their costs and effectiveness. The model was developed for several European Union countries. The use of this model was illustrated by assessing 2 fictitious, but realistic therapy options: one-time cell-based therapy and a continuous use of biological agents.

**Methods**

Cost utility analysis (CUA) was performed for estimating the potential impact of delaying ESRD in 7 European Union countries. CUA investigates whether a new treatment is good value for money by explicitly comparing its impact on costs and patient effectiveness in terms of QALYs. The relevant population for analysis consisted of CKD stage-4 (CKD4) patients, aged over 20 years, from the following European countries: the Netherlands, United Kingdom, Germany, Italy, Spain, Finland and Hungary. The chosen countries represent a geographical spread across Europe, with considerable differences in transplantation rates and productivity values.

**General Model**

Figure 1 shows the 5 health states in the model: hypothetical patients enter the model in CKD4 and move forward through ESRD to death. A continuous-time state-transition model, with age-dependent fixed state durations, was used. The model was evaluated for different initial ages, and then weighed by age distribution.

Treatment performance was characterized by the delay in disease progression towards ESRD, averaged over the population that the new treatment is applied to. This delay was modelled as a prolongation of the time spent in CKD4, during which new treatment is provided alongside the conventional therapy. In the subsequent ESRD stage, the model differentiates between dialysis and transplantation as RRT, since costs, utility and life expectancy are different for these treatment options. Categorization of RRT was based on the main therapy received. The dialysis option represents ESRD patients who receive dialysis and no transplantation, whereas the transplantation option represents patients who receive transplantation and may in addition also receive dialysis while on the waiting list or after losing the graft.

Costs are presented in euros at 2016 price level. Costs and QALYs were discounted at 3% per year, thus giving less weight to more distant years. The model was programmed in Microsoft Excel 2010 and is available as web content (www.lumc.nl/org/medische-besliskunde/medewerkers/904030438095212).

**Survival Estimates**

Since renal registries only provide information from the moment RRT starts, the clinical epidemiology of earlier CKD stages is poorly understood, particularly with regard to progression between stages. An estimated average duration of 2 years to progress from CKD4 to ESRD was based on previous studies [5–7]. Additional time spent in CKD4 due to the new intervention is input to the model and needs to be determined outside of the model, depending on specific parameters of the intervention under investigation.

To estimate the age distribution for RRT and survival after RRT, data from the Dutch Renal Registry (Nefrovisie/Renine: www.renine.nl), containing information of all Dutch individuals receiving RRT [8], was used. Nefrovisie/Renine provides time-to-death data for both dialysis and transplantation patients aged over 20 years.
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20 years who started therapy from 1995 to 2005. During this period, 14,499 RRT patients were registered, of which 4,642 (32%) received renal transplantation. The median age at RRT initiation was 63 years. The age-dependent remaining life expectancy after RRT (Fig. 2) was estimated using Weibull survival analysis, with shape and scale parameters quadratic in age [9]. The estimates were used for all countries in the analysis, assuming similar survival across countries.

**Table 1.** Country-specific RRT rates and productivity values

<table>
<thead>
<tr>
<th>Country</th>
<th>Annual incidence of CKD4 (per 100,000)</th>
<th>Annual incidence of transplantation (per 100,000)</th>
<th>Transplantation probability, %</th>
<th>Average annual productivity value among the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>14.4</td>
<td>5.1</td>
<td>35</td>
<td>€40,000</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>14.4</td>
<td>3.8</td>
<td>27</td>
<td>€28,000</td>
</tr>
<tr>
<td>Germany</td>
<td>23.6</td>
<td>3.2</td>
<td>14</td>
<td>€43,000</td>
</tr>
<tr>
<td>Italy</td>
<td>22.6</td>
<td>3.3</td>
<td>14</td>
<td>€31,000</td>
</tr>
<tr>
<td>Spain</td>
<td>17.2</td>
<td>4.7</td>
<td>27</td>
<td>€24,000</td>
</tr>
<tr>
<td>Finland</td>
<td>13.0</td>
<td>4.9</td>
<td>37</td>
<td>€42,000</td>
</tr>
<tr>
<td>Hungary</td>
<td>18.8</td>
<td>2.7</td>
<td>14</td>
<td>€9,000</td>
</tr>
</tbody>
</table>

**Fig. 2.** Age-dependent remaining life expectancy.

The probability of RRT patients receiving either dialysis or transplantation depends on national policies, waiting list issues and patients’ age. The average transplantation probabilities by country were estimated from RRT incidence rates (Table 1), which were in turn estimated from RRT prevalence data [10] combined with survival estimates. The relative transplantation probabilities by age were estimated from the Dutch age pattern (on an average 28%, ranging from 87% at 20 years to 0% above 75 years).

**Healthcare Costs**

Costs of the new intervention are input to the model and need to be determined outside of the model, depending on specific parameters of the intervention under investigation. Other country-specific healthcare costs were obtained from published reports [11–15] (Table 2). The costs of conventional therapy in the CKD4 health state also apply to the prolonged CKD4 phase. The annual costs of dialysis are a weighted average of haemodialysis and peritoneal dialysis when sufficient data were available [14, 15]. For those countries and health states for which no cost data were found, the average health state costs over all other countries were used. All costs were converted to euros.

**Utility Values**

Utility for health-related quality of life reflects the value of health, on a scale anchored at 1 (perfect health) and 0 (as poor as death). Utility values (Table 3) were obtained from published reports [3, 14, 16–18]. For comparing health states, only utility values generated by the same assessment method were considered. Since
De Vries/Rabelink/Van den Hout  Nephron 2016;133:89–97
DOI: 10.1159/000446548

The time-trade-off (TTO) was the only assessment method that had been applied to each of the health states, these TTO utilities were selected for the model.

**Productivity Value**

The country-specific average annual productivity value among the general population was calculated using the values of labour participation [19], hours worked per week [19] and labour costs per hour [20] (table 1). Productivity was computed until pension at age 65 years.

The value of productivity among CKD patients was based on a Dutch study showing that 51% of pre-dialysis patients and 24% of dialysis patients participated in the labour market [21]. Compared to the general 75% Dutch labour participation, the relative productivity value for CKD4 was estimated at 68% (51/75) and for ESRD on dialysis at 32% (24/75). As utility after transplantation is very similar to utility in CKD4, the productivity after transplantation was considered to be identical to productivity among CKD4 patients.

Societal costs were estimated using the human capital approach, by subtracting the full productivity value from healthcare costs.

**Results**

Figure 3 shows the patient benefits from delaying ESRD, by country and depending on the treatment performance. By delaying ESRD, the age at RRT commence-

ment is increased and the remaining life expectancy after RRT somewhat decreased (fig. 2). As a result, the gain in life expectancy is about 90% of the duration of the delay. Countries with lower transplantation rates have slightly larger gains in life expectancy (92% for Germany, Hungary and Italy) than countries with higher transplantation rates (89% for the Netherlands and Finland).

Considering the quality of life, a 1-year delay of ESRD results in an average gain of 0.6 QALYs (range 0.60–0.63). Bounded by the pension age of 65 years, the average gain in productivity was considerably lower at 0.3 years (range 0.28–0.35).

**Healthcare and Societal Savings**

Figure 4 shows the estimated healthcare and societal savings from delaying ESRD for the countries analysed, disregarding the costs of the new treatment. In the societal perspective, savings on productivity costs are included in addition to healthcare costs.

Despite the increased life expectancy, the delay of ESRD results in net savings on healthcare. This is because, apart from the new treatment, the annual costs during the initial delay in CKD4 are relatively low, whereas the annual savings due to somewhat reduced life expectancy af-

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**Table 2. Country-specific healthcare costs in 2016 euros**

<table>
<thead>
<tr>
<th>Country</th>
<th>Annual costs in CKD4</th>
<th>Annual costs in dialysis</th>
<th>First year costs after transplantation</th>
<th>Later year costs after transplantation</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>86,000</td>
<td>16,000</td>
<td>16,000</td>
<td>16,000</td>
<td>[11]</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>300</td>
<td>31,000</td>
<td>2,000</td>
<td></td>
<td>[12]</td>
</tr>
<tr>
<td>Germany</td>
<td>63,000</td>
<td>55,000</td>
<td>18,000</td>
<td></td>
<td>[13]</td>
</tr>
<tr>
<td>Italy</td>
<td>40,000</td>
<td>42,000</td>
<td>7,000</td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Spain</td>
<td>36,000</td>
<td>36,000</td>
<td>7,000</td>
<td></td>
<td>[15]</td>
</tr>
<tr>
<td>Finland</td>
<td>50,000</td>
<td>36,000</td>
<td>10,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>500</td>
<td>50,000</td>
<td>36,000</td>
<td>10,000</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Utilities for the health states in the model**

<table>
<thead>
<tr>
<th>Country</th>
<th>CKD4</th>
<th>Dialysis</th>
<th>Transplantation</th>
<th>Elicitation method</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>0.85</td>
<td>0.69</td>
<td>0.86</td>
<td>TTO</td>
<td>[17]</td>
</tr>
<tr>
<td>USA</td>
<td>0.55</td>
<td>0.54</td>
<td>–</td>
<td>HUI</td>
<td>[17]</td>
</tr>
<tr>
<td>USA</td>
<td>0.57</td>
<td>0.69</td>
<td>0.70</td>
<td>TTO</td>
<td>[18]</td>
</tr>
<tr>
<td>Canada</td>
<td>–</td>
<td>0.57</td>
<td>0.81</td>
<td>SF-36</td>
<td>[14]</td>
</tr>
<tr>
<td>Spain</td>
<td>–</td>
<td>0.86–0.93</td>
<td>–</td>
<td>TTO</td>
<td>[3]</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>–</td>
<td>0.74–0.91</td>
<td>–</td>
<td>SG</td>
<td>[3]</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>–</td>
<td>0.58–0.65</td>
<td>–</td>
<td>EQ-5D VAS</td>
<td>[3]</td>
</tr>
</tbody>
</table>
ter RRT are high. The patterns for healthcare savings are similar in different countries, with longer delays leading to higher savings on RRT care. Countries with higher dialysis costs and lower transplantation rates have higher savings because prevented costs after RRT are higher for dialysis than for transplantation. For a 1-year delay of ESRD, savings on healthcare costs range from €2,000 in the United Kingdom to €10,000 in the Netherlands.

Savings on productivity originate from the gain in life expectancy prior to the pension age (fig. 3), and also from the higher productivity in CKD4 than when receiving dialysis. Country-specific differences in savings on productivity are substantial, due to the more than 4-fold difference in annual productivity value (table 1). For a 1-year delay of ESRD, savings on productivity range from €2,000 in Hungary (low on productivity value) to €10,000 in Ger-
many (high on productivity value). The total societal savings range from €8,000 in the United Kingdom to €17,000 in Germany.

**Costs-Per-QALY Analysis**

Based on the expected delay of ESRD due to the new intervention, the model assesses the impact on life expectancy, QALYs, and healthcare and productivity costs. Combined with the expected treatment costs, cost-effectiveness ratios are calculated from either the healthcare or the societal perspective. Figure 5 presents the range of estimated cost-per-QALY ratios, by selecting the delay towards ESRD on the horizontal axis and the treatment costs on the vertical axis. The dashed and solid lines represent the healthcare and societal perspectives, respectively. For example, from a societal perspective, a new treatment providing 4 years delay of ESRD and €100,000 treatment costs has a cost–utility ratio of about €20,000 per QALY. From a healthcare perspective, the cost–utility ratio is closer to €40,000 per QALY.

The curves in the figure represent varying thresholds for how much one is willing to pay for better effectiveness. For example in the United Kingdom, the National Institute for Health and Care Excellence uses a threshold between £20,000 and £30,000 per QALY [22]. In the Netherlands, no formal threshold is used. Yet, similar thresholds of €20,000 or €40,000 per QALY are often used in discussions, or possibly €80,000 per QALY under specific conditions [23]. This approach will be illustrated by 2 fictitious, but realistic therapy options.

**Case 1: One-Time Cell-Based Therapy**

The STELLAR consortium (www.stellarproject.eu) focuses on using stem cells isolated from the kidney for delaying ESRD. Preliminary results obtained within the project suggest a reparative capacity of these stem cells. As this stem cell-based therapy is under development and has not yet been applied in clinical practice, its performance in patient benefit is still uncertain. According to expert opinions, it could be effective in 50% of the patients it is applied to (range 10–100%) and when effective, could delay ESRD by 2 years (range 1–5 years). Therefore, an average delay of 1 year in the analysis is assumed. In addition, the costs of one-time stem cell-based therapy from actual costs for the preparation of bone marrow mesenchymal stromal cells were estimated. It was also estimated that the therapy could be provided at a cost of €7,200, including isolation of material (€800), expansion and preparation (€6,000) and the infusion of stem cells in 2 hospital visits (€400). Costs would be higher when costs of facilities and overhead, intellectual property, or commercial profit margins are included. However, costs could also be lower due to economies of scale.

Figure 5 shows that for the estimated 1-year delay and €7,200 treatment costs, one-time stem cell-based therapy

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**Fig. 5.** Cost-effectiveness of delaying ESRD from the healthcare (dashed lines) and societal perspectives (solid lines), depending on the delay of ESRD and the total costs of the new treatment (averaged over the 7 countries). Case studies 1 and 2 are indicated.
would be cost saving. Therefore, this treatment would be economically acceptable regardless of the specific threshold for acceptable costs. It would still be cost saving if the delay would turn out to be 0.5 years. Applying a threshold of €20,000 and €40,000 per QALY, one-time stem cell-based therapy would be economically acceptable if it delayed ESRD by 0.2–0.5 years.

**Case 2: Continuous Medication Use of a Biological Agent**

For continuous treatment, the treatment costs are incurred over the duration of the CKD4 period, including the delay period. Therefore, treatment costs increase with the delay. Consider a hypothetical drug that is initiated early in the CKD4 stage and that substantially delays ESRD by 10 years (thus extending the CKD4 period from 2 years to 12 years). Costs of the drug are €30,000 per year, with a value of €306,000 over 12 years (discounted at 3%). A 10-year delay is estimated to provide a gain in patient outcome of 5.6 QALYs (fig. 3), with savings of around €54,000 on healthcare costs and €95,000 on societal costs (fig. 4). Combined with the treatment costs, the healthcare and societal cost–utility ratios are estimated at €45,000 and €38,000 euro per QALY, respectively (fig. 5). According to health economic standards in many countries, this would be only just acceptable.

For shorter delays than 10 years, cost-effectiveness would be worse as the costs of the biological agent in the initial 2 years of the CKD4 period have a relatively large impact. For a delay of 1 year, the period of medication use would be 3 years, increasing the cost–utility ratios to more than €100,000 euro per QALY. Therefore, continuous medication use delaying ESRD is unlikely to be cost-effective for prices higher than €30,000 per year.

**Discussion**

In this study, a generic model for early assessment of the cost-effectiveness of delaying ESRD in several European Union countries was developed. The model applies to interventions that can be characterized by how successful they are in delaying the disease progression. In general, a 1-year delay of ESRD was estimated to improve the patient outcome by 0.9 life years and 0.6 QALYs and to improve productivity by 0.3 years. Country-specific differences in access to transplantation had minimal impact on patient outcome, but differences in costs were substantial: for a 1-year delay free of charge, savings on healthcare costs would range from €2,000 in the United Kingdom to €10,000 in the Netherlands and societal savings would range from €8,000 in the United Kingdom to €17,000 in Germany.

This study is the first of its kind to model the generic delay of ESRD for the purpose of early assessment of therapies under development. Studies performing cost-effectiveness analyses for a similar patient population generally compare 2 specific therapies in ESRD [24, 25] or in CKD [7, 26]. Another approach compares several treatment modalities within one model [27]. The current model is a flexible model that allows for varying country parameters and preliminary treatment effectiveness and cost estimates. In doing so, a model suitable for the early assessment of any treatment aiming at slowing the progression to ESRD was developed successfully.

Early detection and treatment of disease is often beneficial. This is also true with respect to delaying ESRD: prolonging the CKD4 stage improves productivity and delaying RRT reduces healthcare costs. Depending on the costs of the new intervention, effective treatment can combine improved patient outcomes with savings to society. Two specific cases were analysed using this model, applying acceptability thresholds of €20,000–€40,000 per QALY gained. The analysis showed that one-time cell-based therapy with €7,200 treatment costs would be economically acceptable if it delayed ESRD by 0.2–0.5 years. It would be cost saving for a delay in excess of 0.5 years. Alternatively, continuous use of a biological delaying ESRD is unlikely to be cost-effective for prices higher than €30,000 per year. These case studies illustrate 2 different approaches. The first case starts from a cost-price analysis and shows whether the intervention would be considered cost-effective at those costs. In the second case study, no cost-price analysis was performed. Instead, the analysis showed the maximum reimbursable price of the new treatment. Such a 'headroom analysis' can provide users details on whether the intervention has a realistic chance of market success.

One of the important mechanisms in the model is how age determines the outcome after RRT. Figure 2 shows that the survival for dialysis is relatively poor. Moreover, it shows a relatively flat curve, indicating that survival after dialysis is primarily determined by disease progression and not by age. As a result, a delay in disease progression almost completely translates into longer survival. The curve for life expectancy after transplantation is steeper, so a larger part of the initial delay is counteracted by reduced survival after transplantation. Thus, in general, delaying dialysis is more cost-effective than delaying transplantation. Therefore, the survival difference be-
between dialysis and transplantation explains why the impact on patient outcomes is more favourable in countries with lower transplantation rates. However, these differences are small.

This study has several limitations. First, early estimates of the effectiveness and costs of a new intervention are uncertain and tend to be too optimistic. Second, the quality of a model can only be as good as the quality of the data it is based on. For several model parameters, data from different countries were not available. For example, the data from published reports from the US on duration of CKD4 [5] and ESRD survival data from the Dutch Renal Registry were used for all countries. To estimate transplantation rates, the national incidence data had to be inferred from the national prevalence data (as separate incidence data for dialysis and transplantation were not reported by national registries), and we were limited to Dutch data on the age pattern of transplantation rates. Moreover, research on the impact of CKD on the quality of life and productivity may not be representative across countries and cost differences within countries may be just as large as cost differences between countries. Third, the model is a crude model based on averages. It ignores more subtle relationships like the impact of the new treatment on the quality of life or the impact of prolongation of CKD4 on the transplantation rate and subsequent survival after RRT. For specific applications, models that are more sophisticated may need to be constructed. Fourth, the uncertainty of the model was not formally explored. Formal uncertainty analysis on the parameters of the model would be complex and would provide no information on the structural uncertainty of the model, or the uncertainty of the new intervention’s preliminary estimates of the effectiveness and costs that are input to the model. For specific applications, the model is available as web content to perform several types of scenario analysis (www.lumc.nl/org/medische-besliskunde/medewerkers/904030438095212).

Conclusion

This study provides evidence for the economic potential of therapies delaying ESRD. A 1-year delay of ESRD improves patient outcomes similarly over all countries assessed. Country-specific differences in costs are substantial. Generally, continuous use of medication is unlikely to be cost-effective for prices higher than €30,000 per year. The developed model provides developers and researchers information about the market success rates of treatment options at an early stage.

Acknowledgments

The research leading to these results has received funding from the European Community’s Seventh Framework Program (FP7/2007–2013) under grant agreement number 305436 (STELLAR).

We would like to thank Frans van Ittersum and Aline Hemke for kindly providing data from Nefrovisie/Renine.

Disclosure Statement

The authors declare no conflicts of interests.

Statement of Ethics

No approval was required.

References


