Optimal dosing strategy for prothrombin complex concentrate
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CHAPTER 4

A low fixed dose of prothrombin complex concentrate is cost effective in emergency reversal of vitamin-K antagonist therapy

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The management of bleeding patients on vitamin K antagonist (VKA) therapy is a common clinical challenge. Current ACCP guidelines recommend the use of Prothrombin Complex Concentrates (PCCs) for rapid reversal of VKA induced coagulopathy (1). While efficacy and safety of PCC are well established for VKA reversal, a well-defined dosing strategy is still lacking. Recently, we studied the effectiveness of a low fixed dose regimen of 1040 IU F IX PCC compared to variable dosing to counteract VKA associated emergency bleeding (2). This prospective study showed that low fixed PCC dose was non-inferior to variable dosing in terms of clinical outcome. In reaching the target INR, defined as INR<2, the fixed dose was non-inferior in patients with an initial INR below 7.5, but not in patients with a higher INR. An important question from both a clinical and costing point of view is whether additional interventions were needed in the fixed dose cohort to reach the non-inferior outcome. The costs of additional interventions (i.e. other blood products, invasive interventions, or more often admission to an intensive care unit) may nullify any cost savings to be gained from a lower PCC dose. Therefore we performed a cost analysis, where we evaluated the direct medical costs in all patients admitted through the Emergency Room (ER). To prevent bias in estimating the costs of VKA-related bleeds we excluded patients already hospitalized for other indications. Cost-effectiveness was calculated using two decision tree models [Figure 1]. In model A reaching the target INR was modeled while model B was only based on the clinical outcome. Only direct medical costs during hospitalization from ER admission to discharge or death were included. These costs included PCC and blood transfusion, endoscopic and/or surgical treatment, mortality, medical ward and/or intensive care stay costs. Unit costs were based on Dutch hospital source (year 2011 prices) and reference prices (inflated to 2011) (3). Analyses included Monte Carlo simulations, base-case analyses and sensitivity analyses in which worst-case scenarios were adapted for the fixed dose parameters to prevent any potentially coincidental finding. Cost analyses were performed in 137 patients. Their characteristics and outcomes were comparable with the whole population in the clinical study. PCC costs accounted for 13% and 17% of the total hospital costs in the fixed
Figure 1: Decision tree models
Model A - Decision tree representing the results of the clinical study with respect to target INR reached (<2) and clinical outcome (positive/negative) Model B - Decision tree representing the results of the clinical study with respect to clinical outcome (positive/negative) * represents the outcome group regarded as ‘successful treatment’ in each model

and the variable dose cohorts, respectively. In the majority of patients target INR was reached with a positive clinical outcome (N fixed dose: 50/59, variable dose: 64/78). These patients in the fixed dose cohort received more often FFP (0.30 versus 0.09 units/patient) but had a shorter mean length of stay at a general ward compared to the patients in the variable dose cohort (7 versus 10 days). For patients who did not reach the target INR (N fixed dose: 3/59, variable dose: 4/78) an additional €3177 was spent on average
to obtain a positive clinical outcome in the fixed dose strategy compared to the variable dose. This higher amount is mainly due to higher RBC and FFP transfusion, more endoscopic treatments, ICU stay and mortality in the fixed dose cohort. Using model A the mean costs per patient were €5774 (Sd=294) for the fixed and €7408 (Sd=365) for the variable dose, resulting in €1634 savings per patient with the fixed dose strategy (table 1). Costs per successfully treated patient (mean costs per patient / probability to obtain a successful treatment) were €6929 (Sd=352) and €9029 (Sd=445), for fixed and variable PCC dosing, respectively (p<0.001).

Disregarding the target INR reached (model B), mean costs per successfully treated patient were similar to those in model A. In model B three worst-case scenarios were conceptualized for the sensitivity analyses. In worst-case scenario #1, we maximized the length of stay in a medical ward for patients with a positive clinical outcome in the fixed dose cohort from 7 days to 10 days conform the length of stay in the same outcome group of the variable dosing regimen. While this analysis increased the costs, the fixed dose strategy still remained the less costly strategy (€7018 for fixed versus €7392 for variable dose strategy; 95% CI for cost difference 277 to 497; p<0.001). Two additional worst-case scenarios assessing the impact of differences in mortality and in volumes of additional interventions confirmed robustness of our findings. From a clinical point of view, some notable differences between the outcome groups were seen. In the fixed dose cohort a higher use of FFP was seen, which we ascribe as a direct consequence of the PCC strategy. Furthermore, a lower mortality rate and shorter length of hospital stay was seen in this cohort, which could both be a consequence of the PCC strategy or a coincidence. By performing sensitivity analyses, we explored the robustness of our results regarding these differences in which the overall conclusion constantly remained valid. Interestingly, we did see the same trend in higher mortality rate in the variable PCC dose regimen compared to the low fixed dose regimen in our previous pilot study which was performed in one Dutch hospital site (4).
**Table 1:** total costs of VKA associated bleeding in the studies cohorts

<table>
<thead>
<tr>
<th></th>
<th>fixed dose strategy (N=59)</th>
<th>variable dose strategy (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Sd</td>
</tr>
<tr>
<td><strong>Model A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean costs per patient (C)</td>
<td>5774</td>
<td>294</td>
</tr>
<tr>
<td>Probability of a successful treatment** (P)</td>
<td>0.83</td>
<td>-</td>
</tr>
<tr>
<td>Mean costs per successfully treated patient (C/P)</td>
<td>6929</td>
<td>352</td>
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<tr>
<td><strong>Model B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean costs per patient (C)</td>
<td>5759</td>
<td>299</td>
</tr>
<tr>
<td>Probability of a successful treatment** (P)</td>
<td>0.95</td>
<td>-</td>
</tr>
<tr>
<td>Mean costs per successfully treated patient (C/P)</td>
<td>6062</td>
<td>315</td>
</tr>
<tr>
<td><strong>Sensitivity analyses</strong></td>
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<td></td>
</tr>
<tr>
<td>worst case #1</td>
<td>Mean costs per patient</td>
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<tr>
<td>worst case #2</td>
<td>Mean costs per patient</td>
<td>5816</td>
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<tr>
<td>worst case #3</td>
<td>Mean costs per patient</td>
<td>5910</td>
</tr>
</tbody>
</table>

**In model A a successful treatment is when a patient has both target INR reached and a positive clinical outcome. In model B a successful treatment is when a patient has a positive clinical outcome, regardless of whether or not the target INR is reached. Worst case scenario #1: maximal length of stay in a medical ward for patients with a positive clinical outcome. Worst case scenario #2: maximal mortality for patients with a negative clinical outcome in both cohorts Worst case scenario #3: maximal volume for all parameters in patients with a negative clinical outcome**
In summary, our cost analyses showed that a cost reduction in PCC with a low fixed dose strategy did not coincide with a cost increase due to utilization of other treatment options for VKA associated bleedings. Furthermore, by treatment of these bleeding emergencies with a low fixed PCC dose strategy, on average €1634 per patient to €2100 per successfully treated patient was saved compared to a variable dosing strategy. The robustness of this finding was confirmed in sensitivity analyses.

Costs should not be the driving force behind selecting the right treatment. However, taking costs into account is becoming increasingly important when choosing between alternatives. Especially since PCC usage is more and more being explored for counteraction of the new oral anticoagulant therapy.

Taking into account the effectiveness of the low fixed dose of PCC in our previous study and the presented cost analyses, we conclude that a low fixed dose of 1040 IU IX PCC is more cost-effective in emergency reversal of VKA than a high variable dosing strategy.
REFERENCES


