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### A low fixed dose of prothrombin complex concentrate is cost effective in emergency reversal of vitamin K antagonists

The management of bleeding patients on vitamin K antagonist (VKA) therapy is a common clinical challenge. Current American College of Chest Physician (ACCP) guidelines recommend the use of prothrombin complex concentrates (PCCs) for rapid reversal of VKA-induced coagulopathy.<sup>1</sup>

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.<sup>2</sup> 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 less than 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, in which 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 2 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).<sup>3</sup>

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 and the variable dose cohorts, respectively.

In the majority of patients, target INR was reached with a positive clinical outcome (N. fixed dose 50 of 59, variable dose 64 of 78). These patients in the fixed dose cohort more often received FFP (0.30 vs. 0.09 units/patient) but had a shorter mean length of stay on a general medicine ward compared to the patients in the variable dose cohort (7 vs. 10 days). For patients who did not reach the target INR (n. fixed dose 3 of 59, variable dose 4 of 78) an average additional 3177 euros were spent 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.

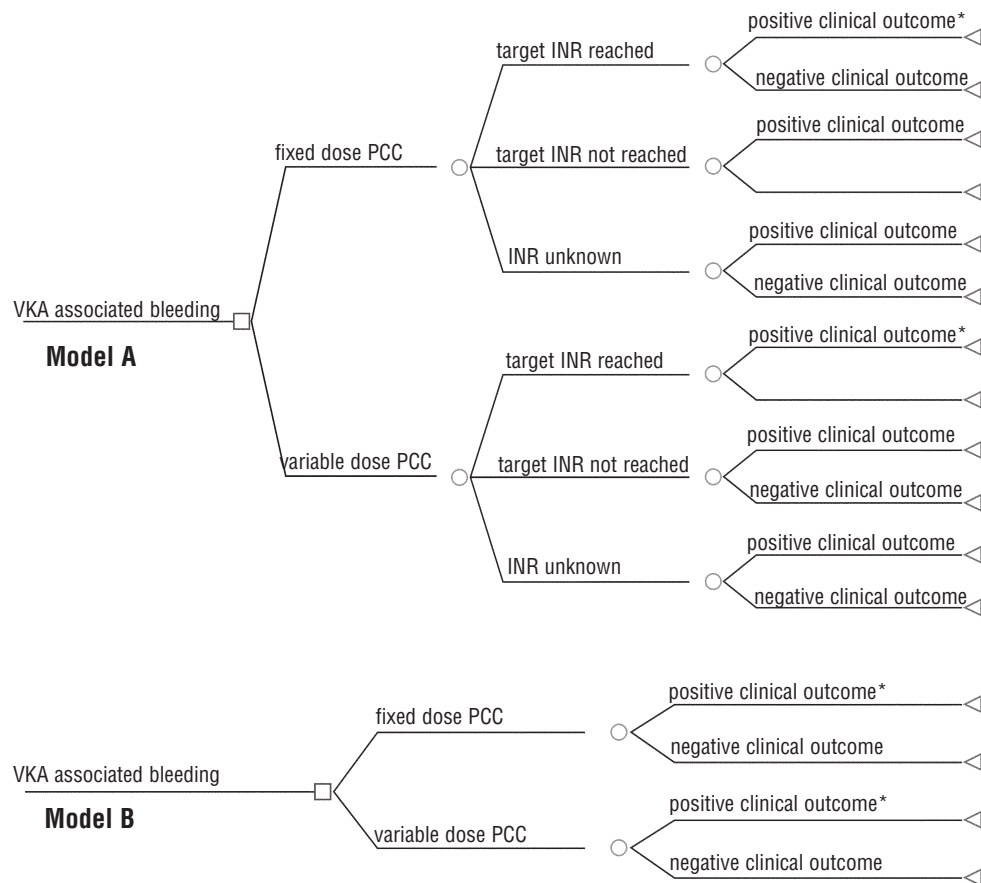
Using model A, the mean costs per patient were 5774 euros (SD 294) for the fixed and 7408 euros (SD 365) for the variable dose, resulting in savings of 1634 euros per patient with the fixed dose strategy (Table 1). Costs per successfully treated patient (mean costs per patient/probability of successful treatment) were 6929 euros (SD 352) and 9029 euros (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 on a general medicine ward for patients with a positive clinical out-

**Table 1.** Results of the cost-effectiveness analyses in both Model A and Model B.

	Fixed dose strategy (N=59)		Variable dose strategy (N=78)		
	Mean	SD	mean	Sd	
<b>Model A</b>					
Mean costs per patient (C)	5774	294	7408	365	
Probability of a successful treatment** (P)	0.83	–	0.82	–	
Mean costs per successfully treated patient (C/P)	6929	352	9029	445	
<b>Model B</b>					
Mean costs per patient (C)	5759	299	7366	371	
Probability of a successful treatment** (P)	0.95	–	0.90	–	
Mean costs per successfully treated patient (C/P)	6062	315	8185	412	
<b>Sensitivity analyses</b>					
worst case #1	Mean costs per patient	7018	396	7392	369
worst case #2	Mean costs per patient	5816	294	7359	366
worst case #3	Mean costs per patient	5910	299	8290	439

\*\*In model A a successful treatment is when a patient achieves both target INR 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.



**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.

come in the fixed dose cohort from seven days to ten days to conform with 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 approach (7018 euros for fixed vs. 7392 euros for variable dose strategy; 95%CI: for cost difference 277-497;  $P < 0.001$ ). Two additional worst-case scenarios assessing the impact of differences in mortality and in volumes of additional interventions confirmed the 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 to 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 be either 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 on one Dutch hospital site.<sup>4</sup>

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 euros per patient to 2100 euros per successfully treated patient was saved com-

pared 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 alternative therapies, especially since the use of PCC is being explored more and more to counteract the new oral anticoagulant therapy.

Taking into account the effectiveness of the low fixed dose of PCC in our previous study and the cost analyses presented, 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.

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