Promoting the use of Markovian simulation models to study outcomes of thrombectomy after acute ischemic stroke

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Letter to the Editor

In patients at risk for acute ischemic stroke (AIS), simulation studies employing Markov models are increasingly being used.\textsuperscript{1–8} In evaluating both preventive and therapeutic interventions for AIS, the aim of these studies is to determine the ‘typical’ clinical outcomes expected on the long term and to generate estimates of cost-effectiveness. In the field of prevention of AIS, a vast literature has been focused on the pharmacoeconomics of warfarin and novel oral anticoagulants,\textsuperscript{9,10} in the field of treatments for AIS, numerous interventions have been studied in terms of cost-effectiveness including thrombolysis, endovascular interventions, and – more recently – thrombectomy.\textsuperscript{1,2,5–8}

If we consider these modelling tools, most of the simulation software published thus far shares the following characteristics:

(1) Health states: the model implements, with minimal variations across different models, the health states shown in Fig. 1 along with the corresponding transitions from one health state to another. The probabilities of individual transitions are shown in Fig. 1; these probabilities can be adjusted depending on the specific intervention under examination.

(2) Clinical outcomes after AIS: the following outcomes can occur after the first stroke: mRS of 0–2; mRS of 3–5; death (i.e., mRS = 6); the same outcomes can occur also after a recurrent stroke, but patients experiencing the condition mRS of 3–5 after first stroke cannot move to the mRS 0–2 condition after a recurrent stroke.

(3) Life expectancy: the life expectancy attributed to the simulated patients is determined by considering: the age-related and sex-related mortality of a healthy population;\textsuperscript{9} the mortality attributable to stroke (for example, Health Quality Ontario for cause-specific mortality after first stroke\textsuperscript{10} and

Leppert \textit{et al.}\textsuperscript{1} for cause-specific mortality after recurrent stroke). These two factors are separately managed in different sections of the Markov model (see Fig. 1).

(4) Utilities and estimation of QALYs: utility of patients is assumed to be 0.74 for mRS 0–2\textsuperscript{6} and 0.38 for mRS 3–5.\textsuperscript{6} Over the prespecified time horizon (e.g., 20 years), QALYs are computed on the basis of the health states of the model, their utilities, and the corresponding transition probabilities.

(5) Discounting: the annual discount rate (e.g., 3.5\%\textsuperscript{6}) is incorporated in the calculation of QALYs according to standard discounting techniques.\textsuperscript{11}

As regards the practical use of these computer programs, the simulation models published in the past years are essentially based on two software tools: on the one hand, some researchers\textsuperscript{12,13} have used a general-purpose spreadsheet (namely: Excel by Microsoft) to develop these Markovian programs; on the other hand, other researchers\textsuperscript{3,5} have used a specific, commercial program (in most cases: TreeAgePro by TreeAge Software Inc., Williamstown, Massachusetts, USA). The Markovian subroutines written under Excel, as well as the tools developed under TreeAge, share a negative characteristic because they are not freely available. Even NICE does not provide these tools when a technology appraisal is released.

The unavailability of these programming tools is a serious hurdle that limits the scientific advancement of cost-effectiveness research on AIS. Hence, in the present report we have tried to facilitate the application of Markov models in the setting of AIS by developing a simulation software which is an improved version of the tools previously employed for specific research projects.\textsuperscript{3,4} Our simulation model, that can be downloaded from the following link http://www. osservatorioinnovazione.net/papers/thrombectomy.trex, is designed to be run under TreeAgePro version 2011 (or subsequent versions). The input variables for the model are shown in the legend to Fig 1. The output of the program is represented by the estimate of total QALYs per patient accrued over the prespecified time horizon. The software manages only the clinical part of these simulations; however, cost data can be added quite easily by introducing new sections of programming.
States of the Markov model and transition probabilities. The starting point of the simulation model is a Markov node (circled M) from which four branches originate. The first is a transitory health state; the second is functional independence after first stroke, the third is functional dependence after first stroke, the fourth is death. The symbols adopted in this scheme reflect the syntax required by the TreeAge software: O, probabilistic node, terminal node. Variables included in the model: death2str = 0.19 (death rate after recurrent stroke according to Leppert et al.); disc rate = 0.035 (annual discount rate); inc2str = 0.05 (incidence of recurrent stroke according to Leppert et al.); mRS1 = 0.32 (percentage of patients achieving functional independence after first stroke according Health Quality Ontario); mRS3 = 0.33 (the same for functional dependence); mRS6 = 0.19 (death rate after first stroke according to Health Quality Ontario); inc2str = 0.34 (utility after recurrent stroke according to Ganeshalingam et al.); utmild = 0.74 (utility after mild stroke according to Ganeshalingam et al.); utmild = 0.38 (utility after moderate/severe stroke according to Ganeshalingam et al.). Stage = 20 (time horizon in years). The outcomes indicated above refer to the Solitaire thrombectomy device; the two probabilities, whose value is 0.405, are not supported by any specific reference, but reflect expert opinion. RWD, reward (in this model represents the incremental increase in quality-adjusted survival).
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Conflicts of interest: There are no conflicts of interest.

References
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