How country-specific should a country-specific cost-effectiveness analysis be?

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This editorial refers to ‘Cost-effectiveness of dabigatran compared with warfarin for patients with atrial fibrillation in Sweden’†, by T. Davidson et al., on page 177 and ‘Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study’‡, by E. Nikolic et al., on page 220

Two recent cost-effectiveness analyses published in the European Heart Journal add to a growing evidence base regarding the costs and health outcomes associated with dabigatran vs. warfarin for patients with atrial fibrillation and ticagrelor vs. clopidogrel for patients with acute coronary syndromes. Conducted from the perspective of the Swedish healthcare system, both analyses are trial-based economic evaluations augmented with decision models to extrapolate short-term trial outcomes to longer term estimates of costs and quality-adjusted survival. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) provided primary data for the cost-effectiveness analysis of dabigatran vs. warfarin. The Platelet Inhibition and Patient Outcomes (PLATO) trial provided primary data for the cost-effectiveness analysis of ticagrelor vs. clopidogrel. Both trials were large, multinational, randomized controlled studies. RE-LY enrolled 18 113 patients in 44 countries, and PLATO enrolled 18 624 patients in 43 countries.

In both analyses, the analysts relied on clinical data that were pooled across all countries represented in the trial. To inform decision making in Sweden, the analysts applied Swedish unit costs and age-based mortality rates with adjustments for higher hazards among patients with non-fatal events. The PLATO economic evaluation had the advantage of being pre-specified, and the trial included both patient-level documentation of medical resource use for estimates of total medical costs and administration of the EQ-5D for evaluation of health preferences (i.e. quality of life). The RE-LY economic evaluation was more dependent on assumptions to calculate costs and the use of literature-based estimates of quality of life to generate quality-adjusted life years (QALYs).

Results from both analyses indicate positive findings with regard to cost-effectiveness of these novel agents. Davidson et al. reported an incremental cost-effectiveness ratio (ICER) of €7742 per QALY for dabigatran compared with warfarin. This finding is similar to the results of a recent Canadian study, but is more optimistic than results of studies from the UK and the USA (Table 1). For the PLATO trial, Nikolic et al. reported an ICER of €2753 per QALY for ticagrelor compared with clopidogrel. Other independent reports on the cost-effectiveness of ticagrelor vs. clopidogrel for acute coronary syndromes are not yet published.

Economic evaluations for multinational clinical trials

Frequently cited geographic variations in clinical practice patterns and the relative costs of healthcare resources suggest that findings from a cost-effectiveness analysis in one country may not be generalizable to other countries. With adaptation, however, economic evaluations may be considered transferable. To address this issue, national guidelines for economic evaluation agree that a given country’s unit costs should be applied to calculations of costs when adapting an analysis for local decision making. As shown in Table 1, the lower prices for dabigatran in Europe compared with those in the USA were influential and resulted in more favourable cost-effectiveness ratios despite smaller estimated gains in quality-adjusted survival.

Although guidelines for economic evaluation agree on methods for applying local costs, there is less agreement about how to handle treatment effects when they are based on data representing patients outside the country of interest. If the number of enrolled patients is large, country- or region-specific estimates of event rates and treatment effects may be appropriate. However, this approach invariably leads to differences in estimates of treatment effects and reduced statistical confidence. Nevertheless, local...
decision makers often claim that neither patients nor practice patterns in a trial represent local conditions. To balance these concerns, a number of guidelines for economic evaluation suggest that a trial-wide estimate, such as relative risk reduction, should be applied to a country-specific estimate of the baseline risk. This recommendation implies that relative treatment effects are generalizable. Secondary analyses from the RE-LY and PLATO trials call this assumption into question.

Generalizability of treatment effects

Pre-specified analyses of data from the PLATO trial revealed a statistically significant interaction between treatment and geographic region, indicating that the beneficial treatment effects of ticagrelor were more pronounced outside North America. Further analysis revealed that higher dosing of aspirin in the USA compared with the rest of the world was the most important factor in explaining the greater effectiveness of ticagrelor compared with clopidogrel outside the USA.11 Although additional studies are planned to investigate this finding further, it illustrates how local practice patterns can interact with treatment efficacy. Similarly, a recently published secondary analysis of RE-LY data found that patients treated with dabigatran at study sites with better international normalized ratio (INR) control did not experience incremental benefits compared with patients receiving warfarin in terms of composite cardiovascular events (i.e. stroke, systemic embolism, pulmonary embolism, myocardial infarction, and cardiovascular death) and all-cause death.12 A notable finding with relevance for the Swedish cost-effectiveness analysis is that study sites in Sweden had the highest mean time in the therapeutic range with warfarin. Davidson et al. addressed this issue in their decision model by applying lower annual rates of stroke, systemic embolism, and bleeding events corresponding to the top 25% of RE-LY sites with the highest rates of warfarin control. However, they did not report applying lower rates for other cardiovascular events in the warfarin group or modelling the null effects of dabigatran on these events among sites with high-quality INR monitoring.

The PLATO and RE-LY studies provide evidence that absolute event rates can differ across countries in a trial, and that local practice patterns can interact with treatment effects. By extension, healthcare payers have valid concerns about the transferability of cost-effectiveness findings from one country to another, even when local prices are applied. Such concerns have contributed to the emergence of performance-based risk-sharing arrangements in which payment schemes for drugs are tied to health and economic outcomes. As researchers gain greater understanding of the limitations of external validity in projecting trial-wide results from global clinical trials to specific markets, policy makers are likely to increase risk-sharing or post-marketing assessments to help ensure that local healthcare dollars are spent wisely.

Conflict of interest: S.D.R. reports no conflicts of interest relevant to this editorial. She has made available online detailed listings of financial disclosures (http://www.dcri.duke.edu/about-us/conflict-of-interest/).

References


Table I Results of cost-effectiveness analyses of dabigatran vs. warfarin for atrial fibrillation

<table>
<thead>
<tr>
<th>Country</th>
<th>Daily cost of dabigatran, €*</th>
<th>QALYs gained with dabigatran</th>
<th>Cost per QALY, €*</th>
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<td>0.25</td>
<td>68 467</td>
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*Reported currencies converted to Euros: 1 € = US$1.256, CA$1.29, and £0.800.