

Use of Cost-Effectiveness Analysis to Guide the Clinical Implementation of New Therapies

Francesc X. Borrás Pérez

Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

One of the greatest challenges faced by the health authorities of societies with limited economic resources (whatever the nature of these authorities may be) is to determine which therapies or education and prevention programs will be of greatest value to the populations they serve. One of the tools used in their selection is the study of their associated costs and benefits at the population level. In recent years, numerous studies on the cost-benefit ratio, cost-effectiveness or cost-utility of different treatments have appeared in the cardiological literature (presumably performed with the same rigor and biases associated with conventional medical research).

In June 2002, an article by Gaspoz et al¹ comparing the cost-effectiveness of aspirin, clopidogrel, and the combination of these agents in the secondary prevention of ischemic heart disease was published in the *New England Journal of Medicine*. These authors concluded that the equivalence of these drugs in terms of their effectiveness in preventing adverse outcomes bestowed aspirin with an excellent cost-effectiveness ratio; the associated incremental cost was just \$11 000 per life-year gained. In addition, clopidogrel was stated to be indicated in patients for whom aspirin was contraindicated, with an incremental cost of \$31 000 per life-year gained. Administering clopidogrel to all patients (i.e., in place of aspirin), however, or prescribing a combination of both drugs was associated with an incremental cost of \$130 000 per life-year gained—an economically unsuitable result. The cut-off cost used for deciding whether these treatments were economically acceptable was \$50 000 per life-year gained (a limit used until the recent past).

The excellent work of Badia et al² in the present issue of the *REVISTA ESPAÑOLA DE CARDIOLOGÍA* analyzes the cost-effectiveness of adding clopidogrel to standard therapy in patients with acute coronary syndrome in the Spanish setting. In contrast to the above findings, these authors conclude that double anti-aggregation therapy with aspirin and clopidogrel is associated with an incremental cost of €8132 per life-year gained—well below the €30 000 (\$50 000) cut-off value.

So who is right? Are these studies comparable? Has something changed since 2002 to justify this difference? Are cost-effectiveness analyses (CEA) sufficiently explicit and comparable to allow any conclusions to be drawn that can be applied to daily routine? The following lines attempt to answer these questions, albeit in reverse order.

The techniques used for CEA, and their less frequently used big brothers, cost-utility analyses, have been available for many years. However, except for a few small exceptions, they had never been used in the healthcare setting until the 1990s. It was during this time when healthcare costs rose enormously, new technologies appeared every year, new drugs become available—but which were 10-1000 times more expensive than those habitually used—and (very important in this type of analysis) multicentric studies involving thousands of patients were published, thus allowing the probability of the adverse outcomes associated with the therapeutic combinations assayed to be determined with some accuracy.

The basic concept underlying CEA is quite simple. These studies are based on the premise that a new and more effective treatment has become available, but which is more expensive than standard therapy (if this were not the case there would be no need for any such study). The need is to know the excess cost of its use in homogeneous and comparable terms. Although the final aims of CEA may vary, the following lines discuss improvement in survival since this is easier to analyze and is the main interest associated with the use of clopidogrel. Mathematically, the goal of such analyses is

SEE ARTICLE ON PAGES 1385-95

Correspondence: Dr. F.X. Borrás Pérez.
Servicio de Cardiología. Hospital de la Santa Creu i Sant Pau.
Avda. S. Antoni M. Claret, 167. 08025 Barcelona. España.
E-mail: xborras@santpau.es

to simulate the use of the alternative therapies available (using an algorithm of alternatives or decision tree), to allot the costs associated with each strategy (for the maximum number of items known), to calculate the events that occur—as well as those avoided—in each treatment group, and to determine the differences in the financial costs associated with each therapy. The final result is usually expressed in terms of a temporal difference (since the patients who receive the new treatment live longer than those who receive the standard treatment) and a monetary cost (the cost of achieving this improved survival). The units used can vary, although one of the most employed (owing to its intuitive intelligibility) is the cost per life-year gained (with variants such as quality-years or productivity-years). The quantities resulting from the use of the different treatments can be compared among themselves, against a standard, or against limits deemed acceptable by Western economies. Until very recently, all such studies tried to show whether new treatments had a cost per life-year gained of below \$50 000 (or €30 000)—an acceptable figure—or above this threshold—an unacceptable result. This figure is derived from the mean cost (including those of complications and hospital admissions) for one year of dialysis treatment—something society accepts cannot be denied to a patient who, should it not be offered, would face death in the short term. This figure, however, is now becoming obsolete (even though it refers to standard dollars for the year 2001), and there are areas in medicine, such as the use of implantable defibrillators, in which the cut-off value is now \$100 000 per life-year gained³ (although the authors of the cited study give no justification for this increase).

The great problem associated with CEA is the unavailability of certain data and the ambiguity that has to be adopted in some areas. For example, the results of the studies on which CEA are based have defined limits of confidence, some studies are not reproducible, the very concept of the clinical trial focuses attention more on efficacy than effectiveness, and above all cost-effectiveness studies extrapolate the results to periods of time much longer (5, 10, 20, or even 30 years) than the trials from which the results analyzed were taken. To compensate for this limitation, all cost-effectiveness studies involve a sensitivity analysis that includes margins of error for the variables used in the simulation; it therefore calculates cost-effectiveness over contemplated intervals. In other words, it allows the results to be presented in terms of life-years gained for the most “believable” data from the examined clinical trials, as a most conservative estimate (based on the worst case scenario), and as a least conservative estimate (based on the most optimistic scenario). There are no rules for determining these intervals other than the critical selection that authors make with respect to uncertain variables. In this context, most authors apply conservative intervals since it is clear that this is the

weak point of any sensitivity analysis. Critical reading of CEA should always involve a reflection on how the authors justify their sensitivity analyses since it here where uncertainty can be used to promote specific interests. Sensitivity analyses are very important since, in the extrapolation of clinical trial data to real life, an estimate of the minimum effectiveness required for a treatment to be deemed cost-effective must be made available.

Can we, then, respond positively to the first question regarding whether CEA can reliably select cost-effective treatments? Overall we can answer “very probably yes,” although there may be limitations in terms of the quality of results and sometimes a certain reticence (not always justified) concerning their use. It is curious to see how such economically-oriented systems as Medicare make no systematic use of CEA. The implantation of this type of analysis has been resisted⁴ on the grounds of freedom of medical choice (as opposed to the bureaucratic control of financing bodies), the delay in the development of new technologies that such restrictions might impose, and the lack of confidence in the methodology used in CEA. Such a lack of confidence is not exclusive to the USA, and until recently the maxim “a human life has no price” formed part of the protocols of action followed by most doctors. However, it is becoming increasingly well-known that the money required to save a life does not grow on trees, and that in a health system with a closed budget such as that of Spain, spending money on a more expensive technology means that funds have to be diverted from other interventions that could also save lives (e.g., prevention campaigns, the control of risk factors, and other such measures). Using terms akin to those employed by the detractors of increasing spending on new treatments, the last sentence might be written: “With the money spent on saving one life with a new treatment, how many could have been saved by investing that money in health education—perhaps by helping people to quit smoking and thus to avoid a future heart attack?” Although didactic, this question is also demagogic, since it is not clear to what extent health education actually achieves such goals, and it is not even clear whether the money saved by not purchasing a new treatment would actually end up being spent on health education. It can be concluded, however (although not with absolute certainty), that CEA are the most objective instruments for homogenizing the costs of different treatments, and that they are helpful in their comparison (as indeed are tolerability, associated risk and efficacy studies).

The second question posed was whether changes in our knowledge since 2002 now justify the cost-effectiveness of double anti-aggregation therapy with aspirin and clopidogrel. The answer is yes, for a number of reasons, the first of which is the publication of the results of the CURE study, on which the article by Badia

et al is based. The CURE study has been widely cited in the international literature⁵ and indeed in the REVISTA ESPAÑOLA DE CARDIOLOGÍA,⁶ and has had an impact at the level of the production of clinical guides⁷ and the design and analysis of epidemiological studies on the use of treatments.⁸ Briefly, 12 562 patients with non ST-elevation acute coronary syndrome (NSTEMI) were studied, all of whom were treated with aspirin but some of whom were randomly assigned to receive additional treatment with clopidogrel or a placebo for nine months. After one year of follow-up the patients who had received double anti-aggregation therapy suffered significantly fewer (approximately 20%) major cardiac events (death, acute myocardial infarction or stroke) than those who received aspirin alone. At the same time, the CREDO⁹ studied analyzed the role played by double anti-aggregation in patients undergoing interventionist therapy, and also reported a significantly reduced number of major cardiac events. This reduction was the justification for studying the magnitude of the incremental cost of adding clopidogrel to standard therapy with aspirin, and both the authors of the CREDO¹⁰ and CURE¹¹ studies have published in 2005 cost effectiveness analyses of their results. Both analyses were very favorable towards double anti-aggregation therapy and the results are very similar to those reported by Badia et al. The latter authors showed the incremental cost of combined therapy per life-year gained to be €8132 (\$9760), while the CURE study CEA reported a value of \$6475. This difference is not important (both figures are well below the \$50 000 threshold); the small difference between them is due to differences in the methodologies and cost estimators used.

The merit of the work performed by the Spanish group lies in the application of the methodology of CEA to the Spanish setting. Even though Badia et al made assumptions of benefits and survival according to those reported in international studies, the calculation of the resources used were based entirely on Spanish data (from the PRIAMHO¹² and DESCARTES⁸ studies).

The importance of double anti-aggregation therapy (and of CEA in this area) has increased in recent years due to the new medical importance given to NSTEMI. The addition of the determination of troponin levels to the arsenal of techniques for diagnosing acute coronary syndrome, the prognostic implications of this condition, and the redefinition of the concept of infarction, have generated a large number of studies that lie outside the scope of the present journal (readers are advised to make use of specific reviews).¹³ However, the importance of anti-aggregation therapy for NSTEMI cannot be escaped. The recognition of this condition as a cardiological emergency has been paralleled by the development of stents for use in interventionist coronary treatment as well as theories on the appropriateness of opening the coronary artery at the root of the infarction. Different studies (FRISC, RITA) have shown that the

best results are obtained with early intervention, and since 2002 clinical guides have recommended such intervention as clearly superior to the classic paradigm requiring the demonstration of ischemia following an acute episode. Curiously, the cost-effectiveness studies that have been performed in this area have been limited and their circulation not very wide. It is therefore important to mention the recent work of de Winter et al (ICTUS).¹⁴ These authors were unable to show the superiority of early, invasive treatment over selective intervention guided by clinical status. Certainly the results of this work are provocatively different to those of earlier studies, but it should be pointed out that the medical treatment provided to the patients who received the less invasive option was very intense, and that they received both aspirin and clopidogrel. The results of the ICTUS study raise many questions with regard to the validity of accepted clinical guidelines, and highlight the need for cost-effectiveness studies on the therapeutic options available. There seems to be no doubt now about whether anti-aggregation therapy should be administered. Rather, the debate should now center on whether a rapid intervention or an intervention guided by clinical status is more cost-effective.

The final conclusion of all the above is that CEA are an additional tool for both clinicians and healthcare managers, and should be taken into account in the production of clinical action guides. Hopefully, other authors will follow the example of Badia et al. and provide data on other such analyses performed in the Spanish setting.

This editorial cannot end without recommending that readers of the REVISTA ESPAÑOLA DE CARDIOLOGÍA become familiarized with the economic aspects of cardiological attention. The initiative of the *Sociedad Española de Cardiología* to include cost-effectiveness studies in its annual program of ongoing education should be applauded.

REFERENCES

1. Gaspoz JM, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink M, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med*. 2002;346:1800-6.
2. Badia X, Bueno H, González Juanatey JR, Valentín V, Rubio M. Análisis de la relación coste-efectividad a corto y largo plazo de clopidogrel añadido a terapia estándar en pacientes con síndrome coronario agudo en España. *Rev Esp Cardiol*. 2005;58:1385-95.
3. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med*. 2005;353:1471-80.
4. Neumann PJ, Rosen AB, Weinstein MC. Medicare and cost-effectiveness analysis. *N Engl J Med*. 2005;353:1516-22.
5. CURE Steering Committee. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation. *N Engl J Med*. 2001;345:494-502.

6. Valentín V. Clopidogrel en el síndrome coronario agudo sin ascenso del segmento ST. Repercusiones clínicas del estudio CURE. *Rev Esp Cardiol*. 2001;54:1127-34.
7. Patrono C, Bachmann F, Baigent C, Bode C, de Caterina F, Charbonnier B, et al. Documento de Consenso de Expertos sobre el uso de agentes antiplaquetarios. *Rev Esp Cardiol*. 2004;57:963-80.
8. Bueno H, Bardají A, Fernández-Ortiz A, Marrugat J, Martí H, Heras M, en nombre de los investigadores del Estudio DESCARTES. Manejo del síndrome coronario agudo sin elevación del segmento ST en España. Estudio DESCARTES (Descripción del Estado de los Síndromes Coronarios Agudos en un Registro Temporal Español). *Rev Esp Cardiol*. 2005;58:244-52.
9. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, deLago A, Wilmer C, et al; CREDO Investigators (Clopidogrel for the Reduction of Events During Observation). Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-20.
10. Beinart SC, Kolm P, Veledar E, Zhang Z, Mahoney EM, Bouin O, et al. Long-term cost effectiveness of early and sustained dual oral antiplatelet therapy with clopidogrel given for up to one year after percutaneous coronary intervention results from the clopidogrel for the Reduction of Events During Observation (CREDO) Trial. *J Am Coll Cardiol*. 2005;46:761-9.
11. Weintraub WS, Mahoney EM, Lamy A, Culler S, Yuan Y, Caro J, et al; CURE Study Investigators. Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation. *J Am Coll Cardiol*. 2005;45:838-45.
12. Aros F, Cuñat J, Loma-Orsio A, Torrado E, Bosch X, Rodríguez JJ, et al; por los investigadores del estudio PRIAMHO II Tratamiento del infarto agudo de miocardio en España en el año 2000. El estudio PRIAMHO II. *Rev Esp Cardiol*. 2003;56:1165-73.
13. Giugliano RP, Braunwald E. The year in non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:906-19.
14. de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, et al; Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) Investigators. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med*. 2005;353:1095-104.