European Heart Journal (2013) **34**, 1869–1874
doi:10.1093/eurheartj/eht031

CURRENT OPINION

Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association†

Giuseppe Boriani[1]*, Nikos Maniadakis[2], Angelo Auricchio[3], Falk Müller-Riemenschneider[4,5], Giovanni Fattore[6], Francisco Leyva[7], Lorenzo Mantovani[8,9], Markus Siebert[10], Stefan N. Willich[4], Panos Vardas[11], and Paulus Kirchhof[12,13]

[1]Institute of Cardiology, University of Bologna, Policlinico S.Orsola-Malpighi, Via Massarenti 9 40138 Bologna, Italy; [2]Department of Health Services Management, National School of Public Health, Athens, Greece; [3]Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland; [4]Institute for Social Medicine, Epidemiology, and Health Economics, Charité University Medical Centre, Berlin, Germany; [5]Saw Swee Hock School of Public Health, National University of Singapore, Singapore; [6]CERGAS, Università Bocconi, Milano, Italy; [7]Centre for Cardiovascular Sciences, Queen Elizabeth Hospital, University of Birmingham, Birmingham, UK; [8]CESP, Research Centre on Public Health, University of Milano Bicocca, Monza, Italy; [9]CIRFF, Center of Pharmacoeconomics, Federico II University of Naples, Naples, Italy; [10]St Jude Medical, Zaventem, Belgium; [11]Department of Cardiology, Heraklion University Hospital, Heraklion, Crete, Greece; [12]University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK; and [13]Department of Cardiology and Angiology, University Hospital Münster, Münster, Germany

Received 7 July 2012; revised 10 January 2013; accepted 16 January 2013; online publish-ahead-of-print 7 February 2013

Introduction

Healthcare systems face an increasing demand for costly medical interventions. The primary concern of a physician is centred around the best possible treatment for his or her patients, according to patients' requests and expectations. The healthcare system, in contrast, is ideally concerned with the assignment of resources in the best interest of society.[1] Clinicians, public health physicians, economists, commissioners, managers, and politicians need to find ways to balance between what is best for the individual patient and what society can realistically afford.[1–3] Appraisals of the clinical effectiveness, cost-effectiveness, cost-impact, and commissioning of emerging therapies can inform such judgements and decisions.

Health technology assessments (HTAs) provide a means for assessing the clinical and cost-effectiveness of healthcare interventions.[4] The aim of HTAs is to provide unbiased, rigorous, and transparent guidance in the application of emerging therapies, in the background of available resources.[5,6] They are, in effect, a link between clinical evidence and policy-making, informing government agencies, healthcare professionals and administrators, private sector organizations, the healthcare industry, as well as patients, carers, and the general public.

The past decade has witnessed relentless advances in interventional electrophysiology and device therapy. This has mainly been attributable to the development of cardiac resynchronization therapy (CRT),[7] the widening indications for implantable cardioverter defibrillator therapy,[8,9] and the emergence of ablation for atrial fibrillation (AF).[10–12] Characteristically, these therapies involve initial costly equipment and procedures, delivered in a specific infrastructure, while their benefits are generally accrued over the long term. Not surprisingly, such therapies attract scrutiny from commissioners and policy-makers. In this position paper, we review a series of issues that are related to HTAs for catheter ablation and device therapy and that in our view deserve attention.

Health technology assessment: a bridge between evidence and policy-making

The mission of a HTA is to offer guidance to decision-making at the level of the individual clinician, hospital, health economy, and a healthcare system as a whole. The inputs to a HTA come from clinicians, clinical guideline groups, epidemiologists, biostatisticians, economists, commissioners, and health policy-makers (*Figure 1*). To maintain transparency, HTAs count on the participation of other stakeholders, such as paramedical professional groups, technologies' producers, and patient groups. It is this multidisciplinary

†The present consensus statement is an official document of the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC). The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +39 051 349858, Fax: +39 051 344859, Email: giuseppe.boriani@unibo.it

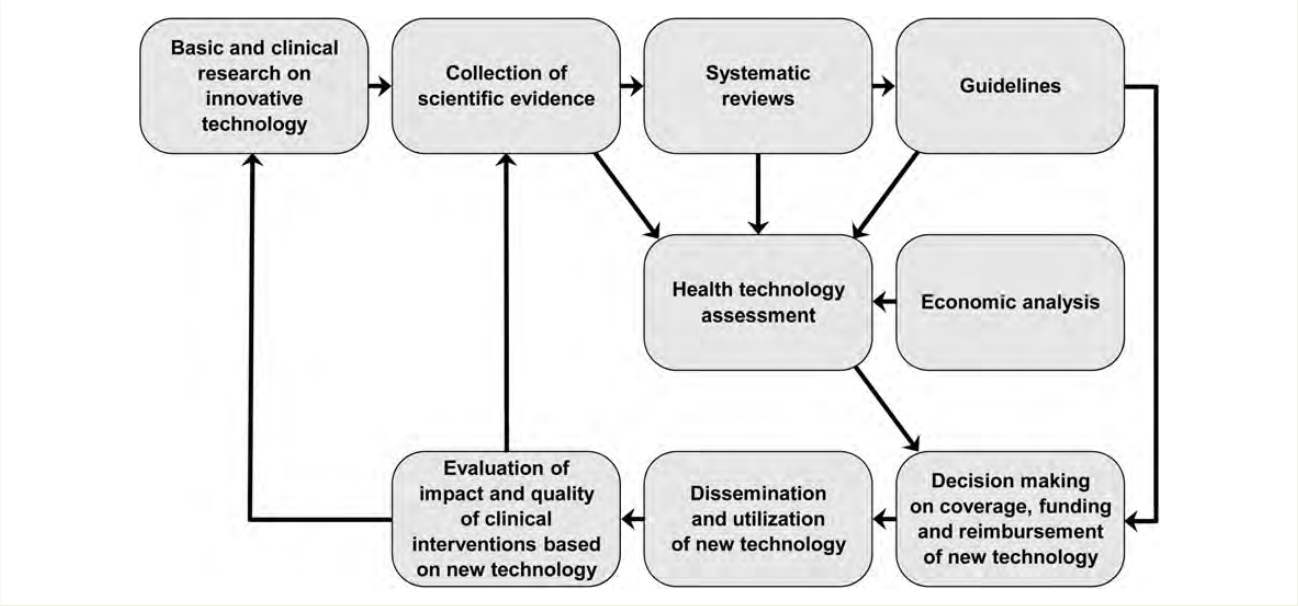

Figure 1 The process of health technology assessment.

approach that has popularized HTAs in the implementation of clinical interventions.[2] Regional policy decision-making as well as regional economics are pivotal in the delivery of healthcare and therefore, regional input is required in the development of HTAs. This is particularly important in communities such as Europe, where wealth, healthcare provision, and costs of medical interventions vary widely. While harmonization of healthcare provision remains an unlikely option in today's Europe,[13] aspirations towards a common ground should not be dismissed. The recommendations from bodies such as the EuNetHTA network[14] (Supplementary material online, *Table S1*) strive to establish such common ground.

The HTA process consists of three phases: scoping, assessment, and appraisal[15] (Supplementary material online, *Table S2*).

Clinical efficacy and effectiveness

The benefits of a given therapy may be measured in terms of efficacy or effectiveness. While both of these are measures of how well a technology improves patients' health, efficacy refers to the benefit of using a technology under ideal conditions, e.g. within a managed randomized controlled trial, whereas effectiveness refers to the benefit of using a technology in the 'real world'. Both measures have their advantages, but reflect different aspects of the therapy and/or the specific population in question.

Systematic reviews have become the most widely accepted means of appraising evidence of clinical efficacy and clinical effectiveness. In recent years, many recommendations on how best to conduct systematic reviews have been developed.[6] The Cochrane Collaboration, the Scottish Intercollegiate Guideline Network Review Group, and the German Institute for Quality and Efficiency in Health Care are among the most prominent organizations that provide guidance on systematic reviews. Tools, such as PRISMA and MOOSE, should also be used in reporting the findings of systematic reviews.[16]

Table 1 Relevant therapeutic effects of interventions in the field of cardiology

Prolonging life
Preventing cardiovascular death/sudden death
Preventing stroke (mainly ischaemic, but also intracerebral bleeding as a rare consequence of anticoagulant therapy)
Improving exercise capacity and quality of life
Preventing arrhythmia-associated symptoms (e.g. palpitations, shortness of breath)
Preventing hospitalizations (e.g. due to worsening heart failure, acute atrial fibrillation, or acute coronary syndromes)
Improving social functioning, improving autonomy and cognitive function (it may lead to re-integration in work processes)

These endpoints of therapy are valid for electrophysiological interventions, such as devices or catheter-based interventions, but also for other interventional treatments. Effects are given in hierarchical order.

Outcomes

The outcomes of medical interventions or programmes may be measured in terms of physiological outcomes, clinician-reported outcomes, caregiver-reported outcomes, or patient-reported outcomes.[17,18] It is accepted, however, that patients are the most legitimate source of information about their own health[18] and therefore patient-related outcomes have been adopted as the most important reference. In the specific field of electrophysiological interventions, the most important therapeutic effects are shown in *Table 1*, in hierarchical order.

Quality-adjusted life years

The quantity and the quality of life are the most basic components of a health outcome measure. The most widely accepted measure is the quality-adjusted life year (QALY), which is the arithmetic product of life expectancy and the quality of remaining life. Accordingly, a year of perfect quality life is worth 1; a year of less than perfect quality life is worth <1, and; death is equivalent to zero. The QALY concept is based on generic measures of quality of life using standardized questionnaires, such as the Short-Form 36 (SF-36) health survey and the EuroQoL (EQ-5D).[3,18] Admittedly, QALYs is based on such generic questionnaires and may not be sensitive to the effects of specific disease processes. Specifically designed scores, such as the Minnesota Living with Heart Failure questionnaire and the NYHA class classification for heart failure, or the AF-QoL (quality of life), and the 'EHRA score' for AF[10,19,20] may better assess the effects a specific disease on the patient.

Costs

The costs include the upfront costs as well as the overall costs over the duration of therapy (*Figure 2*). The costs of therapy should be assessed based on resources, not reimbursement. Consumed resources should be presented in a transparent fashion[3] and modelling should be employed in the quantification of resources that are not directly observed. Estimations of costs and their presentation should encompass direct costs, informal care, and productivity costs and societal costs, respectively (Supplementary material online, *Table S3* and *Appendix S1*).

Cost-effectiveness

An assessment of cost-effectiveness is central to HTAs. The cost per QALY has almost universally been adopted as the preferred measure of cost-effectiveness although simpler methods to present economic data have been suggested. The incremental cost-effectiveness ratio (ICER) compares an intervention to the appropriate alternative by making a ratio between the difference in costs and the difference in effectiveness. In cost-utility analysis, the result is expressed as ICER per QALY gained, a measure which has been extensively validated.[3] The ICER is expressed as follows:

(Costs Treatment A − Costs Treatment B)/(Outcomes Treatment A − Outcomes Treatment B).

There is no fixed threshold as to what should be considered cost-effective. In the USA, interventions with ICERs <$50 000 (€37 135) are usually considered acceptable; those exceeding $100 000 (€74 270) are considered too expensive, and; the range from $50 000 to $100 000 (€37 135–74 270) is the 'grey zone'.[3] In the UK, according to decisions taken by the National Institute of Clinical Excellence (NICE), therapies with an ICER per QALY ≤ GBP 15 000 (€22 261) are considered cost-effective, whereas special reasons would be required for supporting technologies with ICERs > GBP 30 000 (€44 523).[1] No single figure is available for Europe, but a benchmark of €40 000

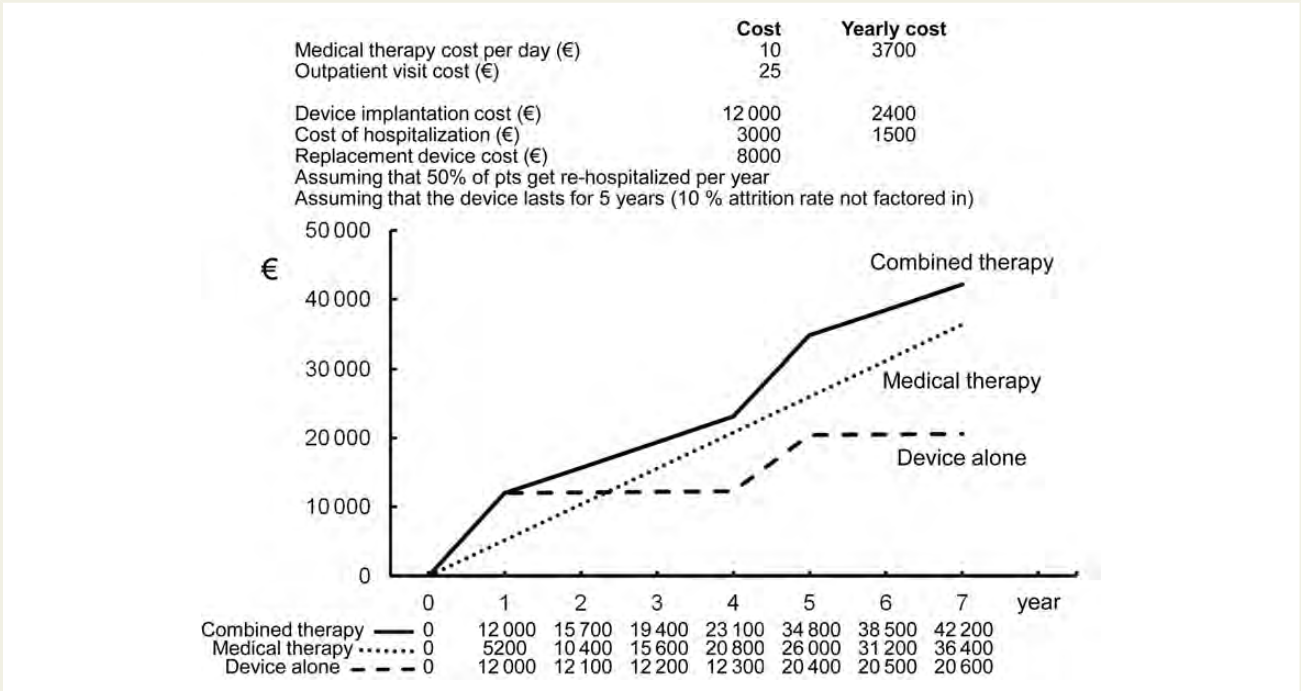

Figure 2 Calculation of cumulative cost (in €) over time of a device therapy (e.g. for preventing sudden cardiac death) vs. pharmacological therapy (costs are presumptive). The costs linked to device therapy show an asymmetrical, discontinuous distribution, while drug therapy is characterized by a progressive increase of cumulative costs, with a constant slope. Cumulative costs are calculated considering device therapy and medical therapy alone, as well as combined prophylactic therapy (drugs and device).

($53 824) appears to be consistent among the wealthiest countries.[3]

Sensitivity analyses

The 'reference case' in cost-effectiveness analyses is a relatively crude figure that reflects the patient characteristics, device technology, implantation techniques, post-operative care, medical therapy, and long-term follow-up that pertain to the study population, be it a trial or a registry. To be meaningful for context-specific decision-making, reference cases must be adjusted to reflect current guidelines, current, and 'real world' practice. Sensitivity analyses provide a means of assessing uncertainty and of adjusting reference to particular situations. These analyses consist of varying key parameters and calculating the effects on the ICER.[3]

Perspective

The type of resources to be taken into account in an economic evaluation largely depends on the perspective, or the viewpoint, from which an analysis is conducted.[3,6,21] Clinical efficacy data are almost universally the product of large, multicentre randomized clinical trials. In the case of rare diseases, it may be technically impossible or ethically unjustifiable to conduct randomized clinical trials, so a less solid evidence may be available. Cost-effectiveness analyses are often undertaken combining evidence from different sources, including registries and observational studies. Often, these sources come from different countries with different healthcare systems, equipment, and procedure costs as well as different reimbursement schedules.[22,23] To make a HTA relevant to different European countries, their particularities, in terms of healthcare funding and organization, must be reflected throughout the HTA process. While continuous efforts should be made to reduce differences in healthcare provision across Europe, some differences are inevitable. Notwithstanding, a publicly funded healthcare system should be adopted in the reference case.

Potentials and limits of cost-effectiveness

While cost-effectiveness strongly influences the conclusions of HTAs, it does not imply public priority.[1,2] It is true that therapies that are most cost-effective are likely to be applied first. There will, however, be clinically and cost-effective therapies that cannot be implemented for other reasons. There may, for example, be too many individuals eligible to have it, or there may be technical and logistical reasons precluding implementation. On the other hand, an intervention that is not cost-effective may be worth supporting if there is no alternative therapy. Clearly, implementation of a new therapy depends on factors other than cost-effectiveness.

Cost-effectiveness analysis provides an analytical approach to identify the economic value of interventions and to prioritize them. While in theory it can be used to, automatically produce decisions about funding technologies, it is advisable to see it as one of the dimensions to be investigated in HTAs and thus as one of the inputs to multicriteria decision-making. In addition to efficacy, effectiveness, and cost-effectiveness other important criteria include equity, organizational concerns, and ethical implications associated to the use of the technology.

The factors influencing economic evaluations in interventional electrophysiology and device therapy and the evaluation of available HTA are discussed in the Supplementary material online, *Appendix S2*).

When to undertake a health technology assessment?

There are no hard and fast rules as to the timing of an HTA. The advantage of an early HTA is the abandonment of technologies or interventions that are ineffective or harmful. On the other hand, an early HTA may be misleading, particularly for therapies that are evolving and for which long-term outcomes may not be known. All HTA bodies across Europe that are partners of EUnetHTA (Supplementary material online, *Table S5*) are focused on an analysis of the respective healthcare contexts in order to determine the best timing and the best possible way in which an HTA may have a positive influence on policy processes. The European Heart Rhythm Association (EHRA) is committed to be a stakeholder in this field, providing independent assessments of both technical and clinical issues.[24] As an organization of the European Society of Cardiology (ESC), EHRA will consult with other ESC organizations (e.g. coronary or valvular interventions) in the various issues that it should adopt in assessing HTAs.

Recommendations

On the basis of the above, we make the following recommendations for agencies that undertake economic evaluations in Interventional Electrophysiology and Device Therapy. The same recommendations may apply to other interventional procedures in cardiology.

Questions and study population

- The scoping, assessment, and appraisal of an emerging therapy should address questions that are relevant to patient groups in which clinical effectiveness has been proved. As outlined in clinical practice guidelines, such patient groups should be defined in collaboration with experienced clinicians.
- A separate appraisal of situations in which there is inappropriate, suboptimal or unintended use of the intervention should also be undertaken. Such situations may include those that are undertaken in clinical practice but which do not necessarily fall under current guidelines.

Outcomes

- Mortality and other outcomes commonly used in cardiology trials should be the main basis to evaluate technologies in HTAs. In addition, for the economic analysis, QALYs should be the preferred summative measure of the clinical outcome. The use of disease-specific quality of life assessments should

be supported by a rigorous validation against the EQ-5D questionnaire.

Costs

- Costs should be based on resources and should be subdivided direct healthcare and non-healthcare costs, costs for informal care and productivity costs; societal costs refer to analyses that include all these costs.
- Explicit reporting of consumed resources, including number of units, manufacturer, model, and cost per unit should be specified.

Economic evaluation

- A lifetime horizon should be adopted in economic evaluations of therapies for chronic conditions, or when a given therapy and the comparator affect survival at different rates. Such is the case for therapies for conditions that have a long-term effect on survival and/or quality of life, such as catheter ablation and device therapy.
- While assuming a lifetime perspective often needs to extrapolate data from trials through models, clinical data taken directly from trials can be used to reflect the average expected duration of the interventional effect. This may range from 4 to 8 years for defibrillator implantations before replacement to 'lifelong' effects for some forms of catheter ablation. Cost of continuous management, including follow-up for devices and management of rare complications of therapy, such as device infections or lead replacement, re-ablation procedures, etc., should be integrated in the analyses.
- The assumptions adopted in modelling should be clearly stated. Every effort should be made to make these assumptions consistent with internationally recognized HTAs guidelines.
- Cost-effectiveness should be measured as Incremental cost per QALY gained according to the standard of cost-utility analysis. Additionally, the social value of interventions should be investigated by techniques aimed to elicit public views on the provision of health care, with the potential for revising priorities set by decision-makers.
- Sensitivity analyses should address uncertainty concerns and the cost-effectiveness of a given therapy applied in accordance with current clinical guidelines. The cost-effectiveness of adhering and deviating from current guidelines should be specifically addressed.
- Sensitivity analyses must assess the effects of varying size of benefits, side effects, time horizon, equipment costs, device longevity nature of procedure, hospital costs of interventions, and co-morbidities.
- An appraisal of the extent to which co-morbidities impact on cost-effectiveness should be undertaken.
- All economic evaluations should consider the arguments for adopting an intervention that is not cost-effective if there is no alternative therapy.
- Device treatments have short life cycle, and frequent change of profile that may facilitate its use, reduce costs, and reduce risks. Therefore economic analysis and HTA should be periodically updated according to the developments of specific technologies. Assessments based on obsolete techniques should no longer be considered.

Budget impact, organizational, and educational issues

- The budget impact of a given therapy must be presented in terms of the upfront costs as well as the overall costs over the duration of therapy.
- Healthcare funding and organizational issues must be reflected throughout the HTA process.
- In the introduction of a new health technology, such as a device or an interventional procedure (i.e. CRT, AF ablation, ventricular tachycardia ablation, percutaneous coronary, and valvular interventions) there is usually a 'learning curve', which will impact on the effectiveness and complications of a specific treatment/intervention. Therefore, issues related to training, education, definition of the appropriate setting for therapy delivery need to be considered and addressed. Moreover, the implementation of a new device or intervention can often have important organizational implications with regard to referral (e.g. hub-and-spoke models).Therefore, adaptation and contextualization with regard to specific environments, reorganization of access to laboratories need also to be considered. The role of scientific professional organizations in providing adequate inputs is crucial.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: N.M., F M-R, L.M., and S.N.V. had no potential conflict of interest to declare. G.B.: Speaker's fees from Medtronic. A.A.: Consulting Fees/Honoraria from Medtronic, Biotronik, St Jude Medical, Sorin, EBR System, Philips, Merck, Abbott, Biosense Webster, BMeye, Impulse Dynamics, Spectranetics. G.F.: Consulting fees from Medtronic, Sanofi-Aventis, Boeringher Ingelheim, Novartis. F.L.: Consulting Fees/Honoraria from Medtronic, Boston Scientific, St Jude Medical and Servier. M.S.: Employee of St.Jude Medical. P.V.: Consulting Fees/Honoraria from Bayer, Boehringer, Medtronic; Research Grants from Astra Zeneca, Servier, Sanofi Aventis. P.K.: Consulting Fees/Honoraria from 3 M Media, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, OMRON, MEDA Pharma, Medtronic, Sanofi Aventis, Servier, Siemens, TAKEDA, Baker AG; Research Grants from 3 M Medica/MEDA Pharma, Cardiovascular Therapeutics, Medtronic, OMRON, Sanofi Aventis, St Jude Medical the German Federal Ministry for Education and Research (BMBF), Fondation LeDucq, the German Research Foundation (DFG), the European Union.

This document was commissioned by EHRA (European Heart Rhythm Association), and the writing group was selected by the Health Economics and Scientific Documents committees of

EHRA without involvement of industry. Industry was not involved in the planning or production of the document. Within the committees, it was felt that specific insights into the estimation of cost-effectiveness for electrophyiological procedures. M.S. was selected as a participant of this group to provide this specific expertise. M.S. is a Health Economist (MSc in Economics—Ruhr-Universität Bochum and MHE in Master in Health Economics—VLEKHO Belgium) and has previously published well in the field. Hence, he was invited into the group as an expert, not as a representative of St Jude Medical.

References

1. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgements. *BMJ* 2004;**329**:224–227.
2. Maynard A, Bloor K, Freemantle N. Challenges for the National Institute of Clinical Excellence. *BMJ* 2004;**329**:227–229.
3. Maniadakis N, Vardas P, Mantovani LG, Fattore G, Boriani G. Economic evaluation in cardiology. *Europace* 2011;**13**(Suppl. 2):ii3–ii8.
4. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). *Lancet* 2002;**360**: 711–715.
5. Martelli F, La Torre G, Di Ghionno E, Staniscia T, Neroni M, Cicchetti A, Von Bremen K, Ricciardi W and NI-HTA Collaborative Group. Health technology assessment agencies: an international overview of organizational aspects. *Int J Technol Assess Health Care* 2007;**23**:414–424.
6. Fattore G, Maniadakis N, Mantovani LG, Boriani G. Health technology assessment: what is it? Current status and perspectives in the field of electrophysiology. *Europace* 2011;**13**(Suppl. 2):ii49–ii53.
7. Boriani G, Mantovani LG, Biffi M, Schalij MJ, Martignani C, Leclercq C, Bax JJ, Auricchio A. Cardiac resynchronization therapy: a cost or an investment? *Europace* 2011;**13**(Suppl. 2):ii32–ii38.
8. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death—executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Eur Heart J* 2006;**27**:2099–2140.
9. Leyva F, Fernandez Lozano I, Morgan J. Cardioverter-defibrillators: a cost or an investment? *Europace* 2011;**13**(Suppl. 2):ii25–ii31.
10. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**:2369–2429.
11. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace* 2012;**14**:528–606.
12. Kautzner J, Bulkova V, Hindricks G, Maniadakis N, Della Bella P, Jaïs P, Kuck KH. Atrial fibrillation ablation: a cost or an investment? *Europace* 2011;**13**(Suppl. 2): ii39–ii43.
13. EUnetHTA Stakeholder Forum. 2012. Accessed at **http://www.eunethta.net** (5 February 2013).
14. HTA Core Model Handbook. 2012. Accessed at **https://fio.stakes.fi/htacore/handbook.html#domainguidance5** (5 February 2013).
15. National Institute of Clinical Excellence, 2008. Guide to the methods of technology appraisal. **http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf** (5 February 2013).
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;**6**:e1000100.
17. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;**152**:726–732.
18. Valderas JM, Alonso J. Patient reported outcome measures: a model-based classification system for research and clinical practice. *Qual Life Res* 2008;**17**: 1125–1135.
19. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R, Cosio F, Crijns H, Diener HC, Goette A, Israel CW, Kuck KH, Lip GY, Nattel S, Page RL, Ravens U, Schotten U, Steinbeck G, Vardas P, Waldo A, Wegscheider K, Willems S, Breithardt G. Early and comprehensive management of atrial fibrillation: proceedings from the 2nd AFNET/EHRA consensus conference on atrial fibrillation entitled 'research perspectives in atrial fibrillation'. *Europace* 2009;**11**:860–885.
20. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Brandes A, Ezekowitz M, Diener H, Haegeli L, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Aunes-Jansson M, Blomstrom-Lundqvist C, Borentain M, Breitenstein S, Brueckmann M, Cater N, Clemens A, Dobrev D, Dubner S, Edvardsson NG, Friberg L, Goette A, Gulizia M, Hatala R, Horwood J, Szumowski L, Kappenberger L, Kautzner J, Leute A, Lobban T, Meyer R, Millerhagen J, Morgan J, Muenzel F, Nabauer M, Baertels C, Oeff M, Paar D, Polifka J, Ravens U, Rosin L, Steginк W, Steinbeck G, Vardas P, Vincent A, Walter M, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options—a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. *Europace* 2012;**14**:8–27.
21. Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. *Int J Technol Assess Health Care* 2005;**21**:165–171.
22. Boriani G, Burri H, Mantovani LG, Maniadakis N, Leyva F, Kautzner J, Lubinski A, Braunschweig F, Jung W, Lozano IF, Fattore G. Device therapy and hospital reimbursement practices across European countries: a heterogeneous scenario. *Europace* 2011;**13**(Suppl. 2):ii59–ii65.
23. Wolpert C, Lubinski A, Bissinger A, Merkely B, Priori S, Brugada J. Barriers to implementation of evidence-based electrical therapies and the need for outcome research: role of European registries. *Europace* 2011;**13**(Suppl. 2): ii18–ii20.
24. Boriani G, Maniadakis N, Auricchio A, Vardas P. Health economics and outcomes research: a new challenge and field of action for the European Heart Rhythm Association. *Europace* 2010;**12**:601–603.