The cost of new therapies in cardiovascular care

Time for hope or despair for developing countries

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ABSTRACT

In recent years, remarkable therapeutic advances have been made in the field of interventional cardiology with the introduction of statins, thienopyridines, such as clopidogrel and drug-eluting stents. Only a small minority in developing countries can afford these new treatment modalities, while the public health system would be rapidly bankrupted if it were to provide these modalities for all patients who might benefit from it. The purpose of this review article is to provide insight regarding the cost-effectiveness of these new treatment strategies and to address the added costs resulting upon their adoption and their appropriateness in developing countries.

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Cardiovascular disorders continue to be the major source of morbidity and mortality in a large part of the world. Over the last 2 decades, there has been vast improvement in the care of patients with vascular disease due to the continuous expansion and the rapid pace of innovations in pharmacotherapy and medical technology. Remarkable therapeutic advances have been made with the introduction of statins, thienopyridines, such as clopidogrel and drug-eluting stents. The availability of these new treatment modalities though is a major difference in cardiovascular medicine throughout the world. Clearly many of the differences are related to socioeconomic factors. Only a small minority in developing countries can afford these modalities, while the public health system would be rapidly bankrupted if it were to provide for all patients who might benefit from them. Interest in the issue of cost-effectiveness is growing and is becoming even more important since the frequency of interventional procedures is increasing and the cost containment in health care has been recognized as a necessity even in industrialized countries. Simplistic approaches that afford swift, short, and economic procedures are frequently followed in developing countries without any fancy devices or drugs. Despite ignoring many recommendations in the literature, adoption of such strategies often results in significant cost savings without sacrifice of quality or disadvantage for the outcome. One extreme report in this sense came from Switzerland,[1] where 61 patient with acute ST segment elevation myocardial infarction with severe coronary artery disease (CAD) was managed successfully with the use of a single Amplatz left (AL2) guiding catheter, a single guide wire, a single balloon followed by focal stenting to short dilated sections without the use of any femoral sheaths, a pigtail for LV angiogram, low molecular weight heparin, direct thrombin inhibitors or an embolic protection device . In addition, neither an intra-aortic balloon pump nor a puncture site closure device were used. This cost-saving approach was considered sufficient to afford angioplasty for more than 2 additional similar cases. In fact, no specific value ensures that a designation will be " cost-effective"- the decision is relative and depends on the amount of money available to spend on health care. Countries that spend a low proportion of their gross domestic product (GDP) on health care (such as most of arabic and middle east north africa {MENA} region countries) would be expected to use a much lower threshold to define what is economically attractive or "cost-effective" than countries such as the United States of America (USA), that invest many more dollars in health care. Developing countries are less affluent than industrialized ones. Funds of the former are needed to combat infectious diseases, to provide for maternal and child health care and to develop good and clean infrastructure for water and food supplies. The

health care budget in our country is limited, and funds spent extravagantly mean that some other service would have to be shortchanged.Developing countries need to establish local guidelines committees that consider the economic implications of their recommendations and appeal not only to evidence the effectiveness of specific strategies but also to their value from a societal perspective. Cost differentials between products strongly vary from one 'cost concept' to another, such as, acquisition cost, administration cost, hospital cost, and net treatment cost. The comparison of efficacy is even more complicated, as most of the time only indirect comparisons are available, based on different clinical studies, with different durations and definitions of outcomes. The purpose of this review article is to provide insight regarding the cost-effectiveness of new treatment strategies in the field of interventional cardiology on the health care system and to address the added costs resulting upon their adoption and their appropriateness in developing countries.

Sustained clopidogrel (Plavix) therapy for one year after percutaneous intervention (PCI). The recently published Clopidogrel for the Reduction of Events During Observation (CREDO) trial[2] (a large multicenter randomized trial of 2,116 patients), showed that a loading strategy and continuous use of clopidogrel for one year after PCI led to a significant reduction in death, stroke, and myocardial infarction rates compared with patients receiving clopidogrel for one month after PCI. Long-term high cost effectiveness was proved in the setting of all patients receiving PCI[3] and not only those presenting with acute coronary syndrome.[4,5] However, Benart et al[3] pointed to a number of limitations that rendered their results conservative: Applying USA costs based on diagnostic Related Groups (DRGs) both to American and Canadian patients did not account for variation in resource use between these different health systems, failure to include many direct and indirect costs (rehabilitation costs after events, outpatient resource use, lost wages and productivity), the inability to assess the effect of drug-eluting stents on resource use and the use of external database to project life expectancy beyond the end of the trial (Framingham and Saskatchewan models). The improvement in survival in patients with vascular disease secondary to improvement in medical care may not be adequately reflected in these databases. In countries such as those in the MENA region where governments are facing strong upward pressures on health spending – both in terms of per capita spending and total spending due to population growth (that they may well outpace economic growth rates), adoption of such a strategy (Plavix one year for all PCI's) would require significant resource use. Jordan, for example is one of the Middle East and North Africa (MENA) region countries that spends around 9.3% of its GDP on health care (far exceeding the 5% value spent in most of other countries of the same region). As more than 5000 PCI procedures are performed annually here, adoption of such a strategy (Plavix one year for all PCI's) would require approximately 7 million US dollars/year which accounts for approximately 1% of the total medical expenditure (reached in year 2000, 677 million US dollars or 8.3% of GDP[6]). The continuation of the current policy adopted in most public and private hospitals of prescribing plavix for 1 month after using bare metal stents (BMSs) and 3-6 months after using drug eluting stents (DESs), seems more pragmatic and would be sufficient to make BMSs replaced by DESs for all cath lab procedures performed in the country especially, if we assume that the benefit retrieved upon decreasing the percentage of instent re-stenosis by DES usage far exceeds the impact of prolonged plavix prescription in decreasing the incidence of major adverse cardiac events in CAD patients. Alternative solutions that could be advocated would be: 1. To use copies of clopidogrel tablets that are available at much cheaper prices compared to the innovator drug product. Several copies of Plavix have been brought onto the market in some Asian and South American countries (Syria, India, Uruguay, China). However these copies were found to have high levels of impurities and higher levels of the R-enantiomer compared to the reference active S- enantiomer. In addition, 50% of the samples may not comply with the 95-105% limits for content and therefore, considered not of equivalent quality to the innovator drug product.[7] Therefore the safety of these drugs in this setting cannot be guaranteed at all. 2. To substitute the expensive, more popular clopidogrel with its predecessor Ticlopidine for the same purpose. Their corresponding monthly costs are $100 and $62 respectively. Generic Ticlopidine is available though at even cheaper prices (<$ 30/60 tablets). Ticlopidine was approved for use in Canada in April 1991. Since it had become widely used, there had been an increase in the number of published reports documenting potentially fatal cases of hematologic dyscrasia associated with its use, particularly agranulocytosis, aplastic anemia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenia purpura (TTP).[8] Clopidogrel has proved to be equally effective to ticlopidine.[9-12] Despite the fact that it has become more popular as it is accompanied by less life-threatening adverse events, it is thought that the actual incidence of serious hematological side effects other than bleeding is underestimated due to under-reporting.[13] Therefore, the theme in developing countries is that one cannot justify abandoning ticlopidine usage in favor of clopidogrel depending on the safety profile factor alone due to the significant price difference between the 2 products.

Statins for reducing the incidence of coronary artery revascularization. Numerous large, randomized, controlled trials have documented that statin therapy reduces the risk of death or cardiovascular events in patients with or without prior cardiovascular disease.[14-25] More recent studies showed that the larger the statin dosage, the greater the reduction in cardiovascular clinical events.[26-31] A meta-analysis involving 90,056 patients in 14 randomized trials emphasizes that the benefit of statin treatment is not limited to a reduction in coronary disease; but also reduces the incidence of strokes, coronary revascularization, and coronary and total mortality.[32]

Applying the National Cholestrol Education Program revised guidelines reported in May 2001,[33] to the population of the US, it is estimated that 36 million Americans were taking lipid-lowering agents. However, they did not consider the system as the cost of implementing the recommendation. Taking the monthly retail price of an inexpensive statin as an example, and assuming a 5% rate of discounting costs in future years, this recommendation would cost the society more than $500 billion in direct drug costs over the next 20 years. This allocation of resources would cost approximately $1,200 per person per year; that is, a total of 29% of the current annual health care spending per capita (average). The allocation of these resources is expected to result in a lower rate of vascular disease and possibly other disease conditions, but it will almost certainly be at the expense of other potential medical investments. Moreover, based on a post-hoc review of the major statin trials, the Adult Treatment Panel III of the US National Cholesterol Education Program recently concluded: "In high-risk persons, the recommended low-density lipoprotein cholesterol (LDL-C) goal is <100 mg/dl, but when risk is very high, an LDL-C goal of <70 mg/dl is a therapeutic option". This recent advice to seek very low lipid levels of below 70 mg/dl (1.8 mmol/l) for those at especially high risk is thus, an extrapolation of the studies, and of epidemiological data, rather than an evidence-based conclusion derived from the trials.[34,35] The larger the LDL-C reduction, the larger the reduction in vascular disease risk, with a reduction of 1 mmol/l of LDL-C over 5 years reducing major vascular events by 23%.[31] Given the financial costs of statins, it is even more important for physicians with limited resources in developing countries to carefully consider the appropriateness of statin therapy for every patient managed. Moreover, there is a possibility that smaller and lighter Asians may only require low-dose statin therapy, an idea that would be most welcome in the poorer parts of the world. There are reports that low-dose, alternate-day and even weekly statin therapy can produce efficacious and adequate reduction of lipid levels.[36-39] A Japanese study of 51,321 patients found that just 5 mg daily of simvastatin reduced total cholesterol by approximately 20%, and LDL-C by approximately 25%; these effects persisted for the 6 years of the trial.[40] Interestingly, the US Food and Drug Administration noted that serum levels of rosuvastatin amongst Asians was double that of Caucasians, and had advised that rosuvastatin doses should be halved in Asian patients.[41]

Ethnic differences in treatment response are an area of research that governmental bodies must look into, given the unwillingness of commercial companies to further pursue this route of enquiry. Having said this, the Framingham risk table may not accurately estimate coronary risk amongst Asian patients, and may need to be modified to remain relevant for individuals in developing societies.[42-44] On the other hand, as people in these societies attain a more affluent lifestyle and change their dietary habits accordingly, the incidence of dyslipidemia, obesity, elevated blood pressure and coronary disease rise significantly.[45-46] To reduce the burden of these chronic diseases, lifestyle recommendations are needed including weight reduction, engaging in regular moderate-intensity physical activity, and eating a heart-healthy diet, including the Dietary Approaches to Stop Hypertension (DASH) diet. This diet is high in fruits, vegetables, (9 to 12 servings/day) and low-fat dairy products (2-3 servings/day) and low in saturated fat, total fat(<7% of energy, and cholesterol (<25% of energy), therefore it meets each of the major nutrient recommendations that were established by the Institute of Medicine.[47-51] The DASH trial[52] demonstrated that this carbohydrate-rich diet with reduced saturated fat, total fat, and cholesterol substantially lowered blood pressure and low-density lipoprotein cholesterol. One of the key things that has been promoted in the DASH studies is that it is made up of affordable regular cheap foods that are available at most grocery stores. To ensure substantial flexibility and enhance the ability of individuals to consume a heart-healthy diet though, the Optimal Macro-Nutrient Intake to Prevent Heart Disease (OmniHeart) diet was introduced. The OmniHeart trial[53] demonstrated that partial replacement of carbohydrate with either protein (approximately half from plant sources) or with unsaturated fat (mostly monounsaturated fat) can further reduce blood pressure, low-density lipoprotein cholesterol, and coronary heart disease risk. The drawback of the OmniHeart diet is that it is less affordable than the Dash diet so that it will be difficult to popularize it within poor societies. Since many trials clearly show the beneficial effects of simvastatin and lovastatin that are available off patent, it is difficult to advocate using patented statins in the developing world.[14,18-20] An alternative strategy would be to purchase a high-dose formulation of the

expensive patented statin and break the tablet for daily or alternate-day consumption. Breaking Lipitor 80 mg into quarters and taking it on alternate days, producing an effective dose of atorvastatin 10 mg daily was found to be cost-effective.[54] The combination of statins with calcium-channel blockers such as Caduet (amlodipine 5 mg+ atrovastatin 20 mg) and with intestinal cholesterol absorption inhibitor such as Vitorin (simvastatin 20 mg+ ezitimibe 10 mg), is actually less expensive for the combined pill than the price charged for the same doses separately.[55] However, the use of such pills will remain restricted to a limited group of hyperlipidemic patients. Performing research programs that are based on combined therapy are witnessed today with Torcetrapib (combination of cholesterol ester transfer protein inhibitor and atorvastatin) representing the initial example. This policy if adopted by the pharmaceutical industry is expected to have major implications in the pricing and selling of these drugs as the spent budget will afford research on 2 molecules within the same combined pill.

Cost-effectiveness of drug-eluting stents. The commercially available DESs - Sirolimus-eluting (SES) (Cypher, Cordis/Johnson&Johnson), paclitaxel-eluting (PES) (Taxus, Boston Scientific), zotarolimus-eluting (Endeavor, Medtronic Inc.), and tacrolimus-eluting CarboStent (Janus , Sorin company)- have dramatically reduced the rate of restenosis.[56-64] Not only restenosis is less common, but is also more likely to be focal than nonfocal.[57,61,64] Unfortunately, the better clinical efficacy of DESs comes, however, at a substantially higher price[65] than their predecessors BMSs. As the economic burden of new technologies plays an important role in the decision-making process of their acceptance in clinical practice, special attention has been paid to the economic impact of DESs. Quantitative economic data provided by recently published randomized trials[66-68] on single de novo lesions, supports the common-sense notion of DESs, by preventing recurrent cardiovascular events (primarily repeat revascularization), offer downstream savings that warrant the up-front initial greater investment. It is commonly accepted that the use of DESs will be cost-effective for most patients undergoing percutaneous interventions, in particular for those considered having high-risk features for restenosis[65] (diabetes, small vessels, long lesions, in-stent restenotic lesions, chronic total occlusions, ostial lesions and bifurcation lesions), in addition to degenerated saphenous vein grafts and unprotected left main disease stenting. On the contrary, the cost-effectiveness analysis of one prospective randomized controlled trial (BASKET)[69] conducted in Switzerland over a one-year period, indicated that high stent cost of DESs are not compensated for by lower costs during a follow-up of up to 6 months. In the Sirolimus–Eluting Balloon Expandable Stent in The Treatment of Patients with De Novo Native Coronary Lesions (SIRIUS) trial [68] versus TAXUS-IV (the slow-release, polymer-based, paclitaxel-eluting TAXUS stent. The IV trial) [66] treatment with DESs led to substantial reduction in target vessel revascularization (TVR) by 19 versus 12.2 events per 100 patients treated respectively, resulting in a net 1-year cost difference of 300 versus 572 dollars per patient with incremental cost-effectiveness ratios of 1,650 versus 4,678 dollars per TVR avoided and 27,540 versus 47,798 dollars/quality-adjusted life year (QALY) gained respectively. In both trials, the excess duration of dual antiplatelet therapy (at a cost of approximately $100/month) accounted for nearly all the net cost of DES placement at 1 year. Thus, if one were to assume that all patients would receive 1 year of dual antipatelet therapy after stent placement (as supported by the CREDO trial),[2] use of both SESs and PESs would have been nearly cost neutral in their respective trials. The extrapolation of the previous findings cannot be made directly to populations for whom the incremental cost of DESs would be substantially greater than in the SIRIUS and the TAXUS- IV trials, such as very long lesions or patients undergoing multivessel revascularization. In addition, if a significant excess of late events (either stent thrombosis or restenosis) prove to occur beyond the 1-year time limit of follow-up analysis, the cost effectiveness of DESs would be less favorable than suggested by the current available data. Elezi et al[70] performed the first direct analysis between the 2 major DES designs (SESs and PESs) seeking to compare their cost-effectiveness, in relation to their clinical effectiveness when used in patients with CAD. They included 450 patients with diabetes mellitus and in-stent restenosis from 2 randomized studies comparing SESs with PESs (ISAR-DESIRE[71] and ISAR-DIABETES.[72] Assigned costs for the economic evaluation were the initial hospitalization and all subsequent cardiac-related inpatient/outpatient health resources during 9-12 months of clinical follow-up. The economic evaluation was performed from the health insurance system's perspective as an approximation for the societal perspective from which the economic evaluation was performed.

Initial hospital costs were not significantly different between the 2 stents (p=0.53). The follow-up costs were, however, different: 2,684 ± 2,072 euros per patient treated with SES and 4,527 ± 6,466 euros per patient treated with PESs (p<0.001). Total costs also differed at the end of the follow-up: 8,924 ± 3,077 euros per patient treated with SESs and 10,903 ± 7,205 euros per patient treated with PES (p<0.001). There were no differences between patients in the 2-stent groups with respect to mortality and myocardial infarction, however, patients

assigned to the SES group had significantly lower rates of angiographic and clinical restenosis compared with patients assigned to the PES group. The authors concluded that in patients at high risk of restenosis, the use of SESs is associated with lower costs compared with PESs. The cost savings are mainly due to the reduced need of repeat revascularization procedures with SESs.

In health care systems with constrained resources, the use of DESs for patients with CAD might be considered economically unattractive at the current stent prices. The discount prices that are offered to public sector tenders in MENA region countries look encouraging (Express Taxus 1400$, Liberte Taxus 1780$, Cypher 2140$), however, they remain far beyond the real world patient capacity of the countries in this region. The real world here is essentially a low GDP per capita in MENA region with medical expenses per person of <$166 a year except in the Gulf cooperation council countries (GCC) and Lebanon.[73] Moreover, the disparity between the up-front costs of DESs and BMSs is substantially greater in clinical practice than in the published economic analyses where essentially one stent was implanted. In the real world, the average number of stents implanted per case is closer to 2, therefore, magnifying the up-front costs of DESs. The costs rise even more in the context of multi-vessel disease. The CABG is performed in developing countries at a much lower price than in USA and the European Union (average package deal price for general and private sectors in Jordan for example ranges between $7000 - $10000 including all running costs calculated by summing the case fees, procedure fees and per diem charges). Although the real assessment of the relative costs of multivessel DESs versus CABG will have to wait until the completion of the newly launched prospective clinical trials of multi-vessel revascularization,[74,75] data modeling based on ARTS-11 trial[76] suggest that stent strategy will likely have the overall economic advantage.

On the other hand, it is important to emphasize the perspective from which the economic evaluation is performed.[77] The DESs have a much worse impact on hospital finances than on physicians or the payers. Indeed, for the hospitals it is a double jeopardy of losing future revenues as repeat revascularization is avoided and bearing costs of DESs versus BMSs. The deleterious effects of the tightening financial noose on hospitals is clearly more apparent in developing counties, as governments push forward with the reforms to privatize the healthcare sector in order to create a healthcare network that meets the growing demand. The small number of private hospitals in these countries will operate under a squeeze between declining incomes and reimbursements and the rising costs of applying new techniques to improve the quality of their service. Such challenges will inevitably train the burden once again on the public sector where mostly conventional methods of medical services provision are delivered by its side.

There is a bone-deep commitment among cardiovascular doctors in developing countries to keep their profession strong and vital that would contribute to the greater good that they pledged in their Hippocratic oath. The rising costs of applying new pharmaceuticals and devices to improve the quality of their practice are among the most difficult challenges facing their career. Until local guidelines get established in developing countries that use the appropriate threshold to define what is economically attractive and effective, inequities between rich and developing countries can only be rectified through the adoption of certain policies such as using generic forms or copies of the innovative drugs despite the lack of guarantee to their efficacy or safety (clopidogrel, statins), purchasing high-dose formulation of the expensive patented drug and break the tablet for daily or alternate-day consumption (statins), using the old generation of certain drugs rather than new ones (ticlopidine) or otherwise to urge pharmaceutical industry to perform more research programs that are based on combined therapy (torcetrapib), which should have major implications on drug pricing.

Regarding DES high prices, a substantial time lag may be needed until this problem may be confronted with more competitive pricing that will inevitably come into play as new models and new players enter the market.

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