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# Effectiveness and Efficiency of Drug Eluting Stents

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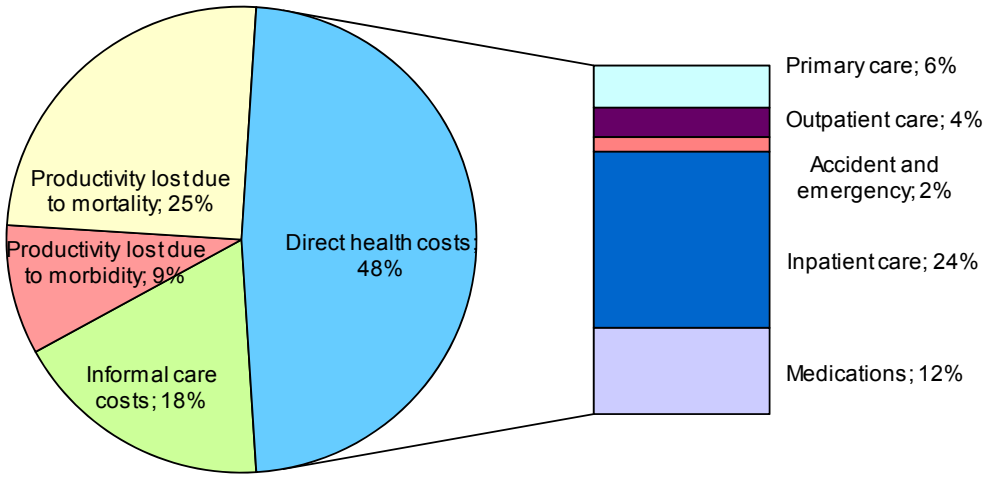
## 1. Introduction

Coronary artery disease (CAD), also known as ischemic heart disease (IHD) and coronary heart disease (CHD), is caused by the narrowing (stenosis) of one or more coronary arteries, due to atherosclerosis, restricting blood flow and reducing the supply of oxygen to the heart muscle. Transient shortages in blood flow and oxygen lead to angina pectoris and chest pain, which may radiate to the left shoulder, arms, neck, back or jaw. Stable angina symptoms do not tend to progress in intensity over time. More seriously, the rupturing of an atherosclerotic plaque (causing a thrombotic occlusion) and stenosis of the vessel can result in acute myocardial infarction (AMI) due to a critical reduction in the blood supply to the heart muscle (myocardial ischemia). High levels of morbidity and mortality associated with this infarction are a consequence of ischemia. It is vital to promptly re-establish coronary blood flow after an infarction, because sustained ischemic damages and injuries to the heart muscle may lead to sudden death or heart failure. In addition to infarction, acute symptomatic manifestations of ischemic heart disease include unstable angina, and less common conditions such as cardiogenic shock and sudden death (Thygesen, 2007).

Cardiovascular disease has a large budget impact, most of which is attributed to coronary artery disease. Therefore, effective treatment strategies are important to reduce associated costs. The total cost of coronary artery disease in the European Union (EU) is estimated to be over €49 billion and can be divided into direct health care costs (48%), productivity losses (34%) and informal care (18%) (Figure 1) (Allender, 2008). Estimated healthcare costs of ischemic heart disease in the EU approaches €24 billion, with approximately 50% of the economic burden due to in-patient care (€12.5 billion) and 25% associated with medication

(€6 billion). In 2006, mortality and morbidity associated with CAD were responsible for nearly €17 billion productivity losses across the EU, whilst informal care costs were estimated to be more than €9 billion (Allender, 2008).

In 2010, ischemic heart disease was the main cause of death worldwide, causing 12.8% of world total deaths (WHO, 2011). Regarding Spain, three out of ten deaths are due to cardiovascular disease, being the leading cause of death even though its incidence has decreased almost a point with respect to the last known data, dating back to 2008 (INE 2011). Specifically, cardiovascular disease has been responsible for 31.2% of the deaths caused in Spain during 2009, resulting in a total of 120,053 deceases. In conclusion, ischemic heart disease is one of the main causes of quality-adjusted life years lost (around 10% of disability), also producing 18% of the Spanish health expenditure, far above respiratory system diseases (13%), and poorly defined signs and symptoms (9%) (Gisbert y Brosa, 2005). Their direct health expenditure in Spain is nearly €727 million, with half of this cost being associated to hospitalizations caused by pathology, 43% to monitoring, and only 6% to pharmacological costs (MsyC, 2003).




Source: Allender, 2008

Fig. 1. Costs of Coronary Disease in EU (2006).

## 2. Revascularization treatment of coronary artery disease: drug eluting stents

Coronary revascularization in patients with atherosclerotic heart disease has emerged as the most accepted method of treatment in the last 50 years, still offering two types of procedures: surgical and percutaneous.

The surgical technique for the implementation of vein and/or arterial grafts was developed in 1960. Since then, the procedure has not undergone many technical changes on the essentials, only an increase in the use of arterial grafts and the achievement of some procedures without extracorporeal circulation in minimally invasive surgery. However, despite the large experience learned over all these years, the results remain operator-dependent and closely related to the amount of procedures performed by each surgeon.

Percutaneous Coronary Intervention (PCI) was first carried out in 1977. It was only reserved for patients with a disease in a single coronary artery, and supported by a surgical team. A clear difference between PCI and surgery is that Evidence-Based Medicine always accompanied interventional cardiology: advances have been supported by randomized multicenter studies before being implemented in all the centers. In the 1980's, PCI spread, but it was a very operator-dependent procedure, using rudimentary catheters and with a high number of complications (acute arterial occlusion in up to 15% of the procedures and restenosis in up to 40-50%). The PCI boom began in the 90's with the development and use of intracoronary stents and the remarkable improvement in balloon catheters, which solved early acute complications freeing the PCI from the surgical services and decreasing the restenosis rates. The BENESTENT study (Serruys et al., 1994) in Europe and the STRESS study (Fischman DL et al., 1994) in America, published in August 1994, gave rise to the spread of coronary stents. PCI stopped being operator-dependent when carried out in centers with a high overall volume, and the dreamt comparison with revascularization surgery began. Until then only the results with balloon catheters in general favored bypass surgery (GABI, EAST, RITA, ERACI, CABRI, BARI studies). Numerous comparative randomized studies were carried out between surgery and PCI in all kinds of situations and with different types of lesions (AWESOME, SoS, ERACI II, ARTS). The results were rather homogenous: there were not significant differences in terms of mortality, except in diabetic patients, between both techniques and differences only appeared in favor of surgery regarding the need of repeating bypass procedures in the short to medium term (Hoffman SN et al., 2003).

Restenosis continued to be the Achilles' heel of PCI despite stents. All efforts were focused on the investigation of antiproliferative drugs linked to stents. In the year 2002, the results from the RAVEL study were published, showing a restenosis rate of 0% at 6 months after implantation of sirolimus-coated stents (Cypher®) (Morice MC et al., 2002). For several years, two kind of drug eluting stents (DES) coexisted largely; the above-mentioned sirolimus-coated stent and another stent coated with paclitaxel (TAXUS®). Many studies and registries were published on both DES in different clinical situations (SIRIUS program, TAXUS program, DIABETES I, ISAR program, COMPARE, etc...), all of them showing similar results in regard to decreased restenosis rates. The first study comparing the results of bypass surgery with PCI using sirolimus DES in patients with multivessel disease was the ARTS II study, which showed that there were not significant differences in the cardiovascular event rates between the group treated with DES and the comparative group treated with bypass surgery of the ARTS I study. However, the ARTS II study was widely criticized, because although the patients with multivessel disease included for DES treatment were more complex, the comparative surgical group was older. Two randomized multicenter studies were designed to compare the results of bypass surgery and PCI with DES in patients with multivessel disease, trying to clarify the controversies; one in diabetic patients, the FREEDOM study, and another one that included all kinds of coronary lesions, the SYNTAX study (Serruys PW et al., 2009). In the latter, 1800 patients with left main or three-vessel disease were randomized to bypass surgery or PCI with Taxus stent, provided that the surgery team and the interventionist cardiology team considered the patient a candidate for any of both interventions. At 12 months, the primary objective of non-inferiority of PCI over surgery regarding MACCE (Major Adverse Cardiac and Cerebrovascular Events) was not achieved (17.8% vs. 12.4% for CABG; P=0.002), mostly due

to the increase in new bypass surgeries in the PCI group (13.5% vs. 5.9%, P<0.001). There were not significant differences in terms of mortality and Myocardial Infarctions (MI), but there was a higher number of strokes in the surgical group (2.2% vs. 0.6% with PCI; P=0.003). After a deep analysis of patients, the study showed that patients with a greater technical complexity derived from their anatomy (SYNTAX score higher than 32) may benefit more from surgery whereas patients with a low (0-22) or medium score (23-32) evolved similarly with both treatments. The analysis of the 705 patients with left main disease showed that those with isolated left main lesion or associated to one-vessel disease benefited more from PCI.

Since 2005, new DES with different drugs (with or without polymers) were incorporated , all of them involving large study projects with a similar design to that applied to the projects of the first generation DES (SIRIUS, TAXUS projects). All the drugs used belong to the "limus" family, which present the lowest Late Loss Index; specifically, tacrolimus, zotarolimus, everolimus, and biolimus. Tacrolimus DES (JANUS®) failed to prove a lower restenosis rate than conventional bare metal stents (BMS). The zotarolimus DES (Endeavour®) was the first second generation stent available. The ENDEAVOR I, II, and III studies showed an excellent balance between the benefits of stent and restenosis reduction since the very beginning, helping the stent to position properly in the European market. Subsequently and with the same drug, the Resolute® stent and the third generation of DES, the Resolute Integrity®, were introduced, following the RESOLUTE FIM study. The Xcience V® and Prime® stents, using everolimus, were developed based on the SPIRIT investigation program, that includes the SPIRIT I, II, III, IV and V studies. As with the zotarolimus stent, we currently have a third generation of everolimus-coated stents already, Xcience Prime® and Promus Element®. Finally, a fifth drug, which is being used at the moment, is the biolimus (Biomatrix® and Nobori® stents) whose results come from randomized studies as LEADERS and NOBORI.

Windecker et al., in The World Congress of Cardiology 2007, triggered an important controversy about the security of DES due to an increase in the occurrence of late subacute occlusions (Windecker S & Meier B, 2007). Kirtane et al., in an analysis of 34 observational studies between BMS and DES including 182,901 patients, showed a reduction in mortality (HR 0.78, 95% CI 0.71–0.86) and myocardial infarction rates (0.87, 95% CI 0.78–0.97) with the use of DES that remains similar after multivariate adjustment (Kirtane AJ et al., 2009). All the studies performed with second and third generation DES prove the results of this meta-analysis with similar subacute occlusion rates to BMS.

Recently, the European Society of Cardiology together with the European Society of Cardio-Thoracic Surgery, have published new guidelines on myocardial revascularization (Task Force 2010). These guidelines state that, taking into account the anatomy, the revascularization has a recommendation of Class I[1] in all cases with left main disease, two or

[1] Classes of recommendations: Class I, Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; Class II, Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; Class IIa Weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb, Usefulness/efficacy is less well established by evidence/opinion; Class III, Evidence or general agreement that given treatment or procedure is not useful/effective, and in some cases may be harmful.

three-vessel disease, proximal anterior descending artery lesion and one-vessel disease with more than 10% myocardial risk. In addition, according to the clinical practice, it is only contraindicated when the optimized medical treatment leaves the patient asymptomatic. Regarding the type of revascularization (surgery or PCI), guidelines suggest an individualized assessment by the cardiology and surgery team of each centre, assuming the general indications. Patients with Syntax high risk score (>33) and two or three-vessel disease have indication Class I for surgery and Class III for PCI. Patients with medium score (23-32) and impossibility of full revascularization by PCI have Class I indication for surgery and Class III for PCI. The rest of cases have both indications.

### 2.1 Stent thrombosis

Thrombosis of a coronary stent is a serious complication, which appears in almost 50% of the cases as transmural acute myocardial infarction, presenting a high mortality rate (Moreno R, 2005). This complication usually takes place during the first weeks after the stent implantation, and especially in the first 24 hours. Chronologically, stent thrombosis is classified as acute (in the first 24 hours after the stent implantation), sub-acute (between 24 hours and 30 days), late (more than 30 days), and as a concept introduced more recently, very late (more than 6-12 months).

The variables associated with a higher incidence of thrombosis are the existence of a visible thrombus before stent implantation, the implantation of more than one stent, left ventricular dysfunction, a suboptimal result, a non-elective stent implantation, small vessels, a residual dissection and a slow flow.

#### 2.1.1 Current recommendations in antiplatelet post-stent treatment

In the initial years of using stents, anticoagulants were initially administered (heparin sodium at first and oral anticoagulation later for several months) in conjunction with acetylsalicylic acid (ASA). In this way, thrombosis rate was reduced to 3-4%. However, this reduction in stent thrombosis rate was at the expense of a high incidence of hemorrhagic complications. In subsequent years, several randomized studies showed that if anticoagulation was replaced with ticlopidine (antiplatelet drug from the group of thienopyridines which works by inhibiting adenosine-deaminase) the incidence of hemorrhagic complications and stent thrombosis decreased (Hall P et al., 1996; Urban P et al., 1998; Schömig A et al., 1996; Leon MB et al., 1998; Bertrand ME et al., 1998). With the appearance of clopidogrel (thienopyridine) the secondary effects associated to ticlopidine disappeared, becoming the drug of choice together with ASA after stent implantation.

According to the Guidelines of the European Society of Cardiology, the double antiplatelet therapy in addition to ASA is recommended during 12 months after stent implantation in patients who suffer acute coronary syndrome, and during 6 months in patients with stable angina (Task Force 2010). Nevertheless, the risk of stent thrombosis with the higher assessed DES is being shown in long-term studies, despite serious doubts. On this point, the new DES is expected to offer advantages, although it will be necessary to get more evidence to eliminate uncertainty. For the second and third generation of DES, the stent thrombosis results are excellent, but the specific time of dual antiplatelet treatment with these devices is unknown and additional studies will be welcome.

## 3. Efficacy and effectiveness of RESOLUTE® DES: preliminary results of REDES registry

Drug Eluting Stents (DES) reduce the risk of restenosis, repeat interventions and re-hospitalization compared to BMS due to the release of potent antiprofilerative drugs from the stent surface. However, despite the success of DES in reducing repeat revascularization procedures, about 5% of patients require repeat procedures within a year. In patients with diabetes or coronary heart disease in small vessels, these rates are higher (Stone GW et al., 2004; Mauri L et al., 2010; Stolk JM et al., 2010). The incidence of myocardial infarction and death attributable to restenosis is minimal, but often causes recurrent angina.

DES have also shown to significantly reduce stent thrombosis, which can be an important clinical problem resulting in an acute myocardial infarction (60-70%), death (20-25%) or emergency bypass surgery (Ayyanatahn S et al., 2009). Nevertheless, the occurrence of late stent thrombosis, between 30 days and a year after stent implantation, is one of the most complex effects of stent placement in general, and of DES in particular.

Due to the above two points, the long-term safety of DES remains an important area of clinical research, especially in avoiding late stent thrombosis (Mauri L et al., 2007). Therefore, clinical studies with different DES are being conducted in order to demonstrate its effectiveness and long-term safety. To date, more than 100 DES randomized clinical trials in 60,000 patients have been performed, but quality varies considerably between different clinical trials, especially regarding the statistical powering and the selection of angiographic criteria instead of primary clinical endpoints. Accordingly, only a small proportion of DES can be recommended based on data from published studies as shown in Table 1 (Task Force 2010).

### 3.1 RESOLUTE® clinical evidence

The coronary stent Endeavor RESOLUTE® is a second generation stent indicated for improving coronary luminal diameter and reducing restenosis in patients with symptomatic ischemic heart disease in de novo arterial lesions of native coronary arteries with a reference vessel diameter of 2.25 to 4.0 mm and a lesion length ≤27mm. Its current clinical program consists of four clinical trials and two multicenter registries: RESOLUTE FIRST, RESOLUTE All Comers, RESOLUTE International, RESOLUTE US, RESOLUTE Japan, and RESOLUTE Asia.

RESOLUTE FIRST is a prospective, multicenter, non-randomized, single arm study of the use of the Endeavor RESOLUTE® stent in patients with symptomatic ischemic heart disease, whose objective was to assess the safety and efficacy in the medium and long term. 139 patients with 140 lesions were included in 12 centers of Australia and New Zealand, and 24-month data are available. The results showed that the cumulative MACE rate at 12 months was 8.5%, and 11% at 24 months. The Target Lesion Revascularization (TLR) rate at one year was 0.8%, and at 12 months there were no Target Vessel Revascularizations (TVR). At two-year follow-up, results showed a TLR, TVR, and Target Vessel failure (TVF) rates of 1.4%, 0% and 7.9% respectively. One possible stent thrombosis occurred in the first year after implantation, however no late or very late thrombosis have occurred (Meredith IT et al., 2009; Meredith IT et al., 2010).

| DES | Eluted drug | Trials and references |
|---|---|---|
| Clinical primary endpoint reached | | |
| BioMatrix Flex | Biolimus A9 | LEADERS (Windecker el al., 2008) |
| Cypher | Sirolimus | SIRIUS (Moses et al., 2003) |
| Endeavor | Zotarolimus | Endeavor II, III and IV (Fajadet et al., 2006; Gershlic el al., 2007) |
| Resolute | Zotarolimus | RESOLUTE-AC (Serruys et al., 2007) |
| Taxus Liberté/Element | Paclitaxel | TAXUS IV and V (Stone et al., 2004; Stone et al., 2005) PRESEUS-WH (Kerelakes et al., 2010) |
| Xcience V | Everolimus* | SPIRIT III and IV (Stone et al., 2009; Stone et al., 2010) |
| Angiographic primary endpoint reached | | |
| Nevo | Sirolimus | NEVO RES I (Ormiston et al., 2010) |
| Nobori | Biolimus A9 | NOBORI I Phase 1 and 2 (Chevalier et al., 2007; Chevalier et al., 2009) |
| Yubon | Sirolimus | ISAR-Test (Mehilli et al., 2006) |

Selection is based on adequately powered RCT with a primary clinical or angiographic endpoint. With the exception of LEADERS and RESOLUTE (all-comers trial), efficacy was investigated in selected de novo lesions of native coronary arteries.
*Promus Element device elutes everolimus from a different stent platform.
DES = Drug Eluting Stent

Table 1. Recommended drug-eluting stents (Task Force 2010).

The randomized clinical trial, called RESOLUTE "All Comers", collected data on more than 15 centers in Western Europe and compared the zotarolimus eluting stent Endeavor RESOLUTE® with the everolimus eluting stent Xcience V (Serruys PW et al., 2010). Between April 2008 and October 2008 data from 1,292 patients with coronary artery disease and chronic stable and acute coronary syndromes were collected: 1,140 patients with 1,661 lesions were assigned to the zotarolimus eluting stent Endeavor RESOLUTE ®and 1,152 patients with 1,705 lesions to the everolimus eluting stent Xcience V. At thirteen month follow-up the Endeavor RESOLUTE ® stent was non inferior to the Xcience V stent with respect to the primary end point of TLF, which occurred in 8.2% and 8.3% of patients respectively (P>0.0001 for non-inferiority). There were no significant differences between the two patient groups in the rate of death from cardiac causes, any myocardial infarction, or revascularization. The rate of stent thrombosis (definitive, probable and possible) was 2.3% in the Endeavor RESOLUTE® DES group and 1.5% in the Xcience V stent (p = 0.17). The lack of strict exclusion criteria in this study allows that the results are representative of actual clinical practice.

Yeung et al., in April 2011 published the 12-month follow-up data from the RESOLUTE US study (Yeung AC et al., 2011): a prospective, multicenter, observational study designed to assess the effectiveness of Endeavor RESOLUTE® DES in patients with one lesion who received a stent between 2.5 and 3.5 mm. Between August 2008 and December 2009 1,402 patients from 116 centers in U.S. were included, with an average vessel diameter of 2.59±0.47 mm and a diabetes prevalence of 34.4%. The results showed that the overall TLF rate at 12 months was 4.7% and cardiac death, myocardial infarction and TLR rates were 0.7%, 1.4% y 2.8% respectively. 0.1% of patients presented stent thrombosis.

Therefore, currently there are published data from three Endeavor RESOLUTE® studies, which have shown to reach a low rate of restenosis revascularization and clinical events such as death, myocardial infarction and stent thrombosis at one-year and two-year follow-up (Table 2). Endeavor RESOLUTE® is an effective and safe stent for the treatment of patients with coronary artery disease in de novo lesions of native coronary arteries.

| | RESOLUTE FIRST (12 months) | RESOLUTE All Comers (12 months) | | RESOLUTE US (12 months) |
|---|---|---|---|---|
| | Endeavor RESOLUTE (1 lesion) | Endeavor RESOLUTE | Xcience V | Endeavor RESOLUTE ( 1 or 2 lesions) |
| | N=130 | N=1,119 | N=1,126 | N=1,376 |
| MACE | 8.5% | 8.7% | 9.7% | 4.9% |
| Death | 2.3% | 1.6% | 2.8% | 1.3% |
| Cardiac death | 0.8% | 1.3% | 1.7% | 0.7% |
| MI | 5.4% | 4.2% | 4,1% | 1.4% |
| Q-wave MI | 0.0% | 0.7% | 0.4% | 0.1% |
| Non-Q-wave MI | 5.4% | 3.6% | 3.6% | 1.2% |
| TLR | 0.8% | 8.8% | 8.2% | 7.4% |
| TVR (non-TL) | 0.0% | 4.9% | 4.8% | 4.6% |
| TVR (TL) | 0.8% | 3.9% | 3.4% | 2.8% |
| TLF | 6.2% | 8.2% | 8.3% | 4.7% |
| TVF | 6.9% | 9.0% | 9.6% | 6.7% |
| Stent Thrombosis (according to ARC, definitive, probable) | 0.0% | 1.6% | 0.7% | 0.1% |

MI: Myocardial Infarction; TLR: Target Lesion Revascularization; TVR: Target Vessel Revascularization: TVF: Target Vessel Failure*; TLF = Target Lesion Failure** ARC = Academic Research Consortium criteria.

*Defined as death from cardiac causes, any myocardial infarction (not clearly attributable to a non-target vessel), or clinically indicated target-vessel revascularization)

** Defined as death from cardiac causes, any myocardial infarction (not clearly attributable to a non-target vessel), or clinically indicated target-lesion revascularization)

Table 2. Summary of published clinical results (Endeavor RESOLUTE®).

### 3.2 REDES registry

Recently was completed the follow-up of a prospective, multicenter, observational, one-arm registry, called REDES, whose objective was to assess the effectiveness and the resource use associated to the Endeavor RESOLUTE® DES in patients with de novo lesions in the native coronary arteries in the Spanish clinical practice. The primary endpoint was defined as the rate of Major Adverse Cardiac Events (MACE) at 30 days, 6 months and 12 months, including cardiac death, myocardial infarction (with or without Q wave), emergency bypass artery coronary graft (CABG) and TLV (repeat CABG or PTCA). Among the secondary endpoints were collected stent thrombosis rates, procedural success, device success, lesion success, TLR, and the identification and quantification of heath resources used in the management of patients at one year after stent implantation.

The Inclusion criteria of patients were patients >18 years, signed informed consent form, drug eluting indication and the decision to use Endeavor Resolute® in all lesions. The exclusion criteria were pregnant or lactating women; patients with hypersensitivity or allergies to aspirin, heparin, clopidogrel, ticlopidine, zotarolimus, rapamycin, tacrolimus, sirolimus, cobalt, nickel, molybdenum or contrast media; patients who have contraindications for antiplatelet therapy and/or anticoagulants; patients with lesions not allowing the full inflation of angioplasty balloon; patients with other DES different from Endeavor Resolute® in other previous lesions; patients with a current medical condition associated with a life expectancy of less than 12 months; and patients who are participating in another study or have completed another study in the last 30 days before registry inclusion. Also, no restriction was placed on the total number of treated lesions, treated vessels or number of stent implanted.

This study allows to know the clinical data and resource use in actual clinical practice with the Endeavor Resolute® stent. The lack of data on resource use and costs associated with treatment of coronary artery disease with DES, as well as their possible alternatives, make more relevant the studies which collect the actual resource use in routine clinical practice and allow to know the associated costs. These studies are the first step to know if stents are an effective and efficient treatment, and help make decisions within the National Health System. During the last years the inclusion of this information in protocols and data collection forms has been increasing in different studies.

#### 3.2.1 Clinical results

Between January 2009 and February 2010 450 patients with 744 lesions from six Spanish hospitals were included. After reviewing the selection criteria, two patients were excluded, leaving 448 evaluable patients with 742 lesions. The exclusions were due to a myocardial infarction within 24 hours before the primary angioplasty procedure that led into a cardiogenic shock and death before obtaining the signed informed consent, and one patient whose clinical history showed a previous DES with another drug.

The mean age of patients was 64.5 years and 78.3% were male, 34.1% had diabetes, 63.4% hypertension, 59.8% hyperlipidemia, and 28.6% smoked at the time of surgery. In addition to clinical risk, 31.9% of patients had a previous myocardial infarction, 20.1% a previous PCI and 4.5% a previous CABG. Most patients had lesions in 1 (55.6%) or 2 (29.9%) vessels, and left anterior descending artery was the most frequently treated. Also, it should be noted that 14.2% of lesions had moderate to severe calcification, 18.9% presented a tortuosity greater than 45 °, and 11.9% bifurcation (Table 3).

| Characteristic | All valuable patients (n=448) |
|---|---|
| Age, yrs | 64.5 ± 10.9 |
| Male | 78.3% |
| Prior MI | 31.9% |
| Q-wave MI | 21.9% |
| Non-Q-wave MI | 10.0% |
| Prior PCI | 20.1% |
| Prior CABG | 4.5% |
| Diabetes Mellitus | 34.1% |
| IDDM | 8.9% |
| Hyperlipidemia | 59.8% |
| Hypertension | 63.4% |
| History of smoking | |
| Current | 28.6% |
| Ex-smoker | 28.3% |
| Family history of cardiovascular disease | 13.4% |
| Worst status | |
| Silent ischemia | 6.9% |
| Stable angina | 28.3% |
| Unstable angina | 31.0% |
| MI | 33.9% |
| Target lesion coronary artery (% total lesions) | |
| Left anterior descending | 46.0% |
| Left circunflex | 18.1% |
| Right | 27.0% |
| Left main | 1.3% |
| Other | 7.6% |
| Number of treated vessels | |
| 1 | 55.6% |
| 2 | 29.9% |
| 3 | 8.9% |
| 4 | 4.5% |
| 5 | 1.1% |
| TIMI flow grade 3 | 83.2% |
| Thrombus | 6.7% |
| RVD, mm | 2.89±0.46 |
| Lesion length, mm | 18.08±10.36 |
| Minimum lumen diameter, mm | 0.73±0.87 |
| %diameter stenosis | 83.22±12.58 |
| Type B2/C lesion | 48.6% |

CABG= coronary artery bypass grafting; IDDM= insulin-dependent diabetes mellitus; MI= myocardial infarction; MLD= minimum lumen diameter; PCI= percutaneous coronary intervention; RVD=reference vessel diameter; TIMI=thrombolysis in myocardial infarction

Table 3. Baseline clinical, lesion and procedural characteristics.

The mean vessel diameter was 2.89 ± 0.46mm and the average lesion length 18.08 ± 10.36mm. The Endeavor Resolute® stent was implanted in 95.5% of lesions treated, with a lesion success of 99.7%, a device success of 95.3%, and a procedure success of 94.7%.

Preliminary results showed that the MACE rate was 1.3%, 3.6% and 4.8% at 30 days, 6 months and 12 months respectively; and the rate of definite, probable and possible stent thrombosis according to the Academic Research Consortium criteria, was 0.7% and 1.4% at 30 days and one year follow-up (Table 4). The 21 MACE, which occurred in 20 patients were 6 cardiac deaths, 4 myocardial infarctions, 11 not programmed revascularizations in the same vessel or lesion treated during the intervention. 5 patients died from probable or possible stent thrombosis, one from a possible heart failure or ventricular arrhythmia not related to the stent, and the remaining non-cardiac death was due to a metastatic renal tumor that was detected a month after the inclusion of the patient in the study. Half of the stent thrombosis occurred within 4 days after surgery and most of restenosis revascularizations were performed by PTCA and only one was performed by CAGB. During the one-year follow-up 13 scheduled PTCA were performed in different vessels than those previously treated.

| | 30 days | 6 months | 12 months |
|---|---|---|---|
| | N = 445 | N = 443 | N = 441 |
| MACE | 1.3% | 3.6% | 4.8% |
| Death | 0.5% | 1.6% | 1.6% |
| Cardiac death | 0.5% | 1.3% | 1.3% |
| MI | 0.5% | 0.7% | 0.9% |
| Q-wave MI | 0.2% | 0.2% | 0.2% |
| Non-Q-wave MI | 0.2% | 0.5% | 0.7% |
| TLR | 0.5% | 1.6% | 2.5% |
| Stent Thrombosis (according to ARC, definitive, probable) | 0.7% | 0.7% | 0.7% |
| Definitive | 0.5% | 0.5% | 0.5% |
| Probable | 0.2% | 0.2% | 0.2% |
| Possible | 0.0% | 0.7% | 0.7% |

MACE = Major Cardiac Adverse Event; MI = Myocardial infarction; TLR = Target Lesion Revascularization; ARC = Academic Research Consortium criteria

Table 4. Clinical outcomes at 30 days, 6 months and 12 months.

If we compare these results with those obtained in the previously published study RESOLUTE All Comers, the MACE and stent thrombosis rates are better. The revascularization rate was lower considering that the proportion of diabetic patients of the REDES study was higher (34.1% vs. 23.5%), but the percentage of lesions in small vessels was lower (39.9% vs. 67.8%). The lack of strict exclusion criteria in this study such as patients with MI, multivessel disease, small vessels, long lesions, bifurcation, or tortuosity make this study representative of routine clinical practice and show actual results of the Endeavor Resolute® stent effectiveness even in patients who had suffered an MI within 72 hours prior to surgery. Therefore, the REDES study results are comparable to and even

better than those obtained in previously published studies showing that the Endeavor Resolute® stent is safe and effective, and considering that a large percentage of patients had a high level of complexity.

### 3.2.2 Resource utilization and costs

The importance of identifying the use of health resources and costs associated with a procedure has increased considerably in recent years; however, there are still few studies that include this part in their objectives. Therefore, the REDES registry, in addition to providing the clinical results of Endeavor RESOLUTE® stent, also included the objective of identifying and quantifying the resource use from patient hospitalization until one year after the surgery in order to know the average cost of the intervention with Endeavor Resolute stent in Spain and at one-year follow-up.

To calculate the costs of the analysis, both the resource data of the REDES study and the e-Salud database were used. The e-Salud database is a private database of health care costs in Spain that can be accessed to obtain the unavailable costs with their maximum and minimum limits.

Table 5 shows the results in more detail. The average cost of the procedure was €7,076.96, but the costs of pre-hospitalization, testing and analysis, and medication before the procedure must be added to have a more realistic view of the patient's cost. These costs were €2,011.93, €1,003.36 and €112.96 respectively. Patients were hospitalized for 2.45 days before the procedure, which involves an additional cost to be taken into account. Only the direct healthcare costs were calculated for the analysis.

| Procedure | % patients | Time (hours) | Cost/Hour | Assumption | Total Costs €2011 |
|---|---|---|---|---|---|
| Hemodynamist | 100% | 1.27 | 33.24 | | 42.07 |
| Nursing | 100% | 1.73 | 15.10 | | 26.16 |
| Catheterization lab. | 100% | 1.73 | 388.21 | Yes | 671.60 |
| Observation unit | 100% | 2.93 | 55.71 | | 163.41 |
| | | **Days** | **Cost/Day** | | |
| Post procedure no ICU | 100% | 1.90 | 820.15 | | 1,557.92 |
| Post procedure ICU | 100% | 0.72 | 1,479.1 | | 1,066.40 |
| | | **Number** | **Unit Costs** | | |
| Standard balloons | 100% | 1.04 | 561.95 | | 584.53 |
| Cutting balloons | 100% | 0.03 | 561.95 | | 17.56 |
| Endeavor Resolute® | 100% | 1.95 | 1,495.33 | | 2,910.55 |
| BMS | 100% | 0.05 | 841.42 | | 39.44 |
| DES | 100% | 0.03 | 1,495.33 | | 43.39 |
| **Complications** | | | | | **117.36** |
| **TOTAL** | | | | | **7,076.98** |

Table 5. Procedure costs

| Analysis and tests | % patients | Average use | Unit Costs | Total Costs |
|---|---|---|---|---|
| Pre-procedure no ICU (days) | 100% | 2.45 | 820.15 | 2,011.93 |
| Cardiac stress tests | 15.18% | 1.03 | 149.13 | 23.30 |
| ECG | 100.00% | 3.07 | 20.73 | 63.57 |
| CK analysis | 74.11% | 2.52 | 3.51 | 6.54 |
| CK-MB analysis | 68.08% | 2.76 | 12.62 | 23.73 |
| Troponin analysis | 81.92% | 2.92 | 15.57 | 37.28 |
| Creatine analysis | 88.17% | 2.03 | 3.84 | 6.87 |
| Eco Doppler | 31.25% | 1.06 | 104.21 | 34.66 |
| IVUS | 6.03% | 1.04 | 77.98 | 4.87 |
| Angiographies | 97.54% | 1.06 | 622.10 | 645.70 |
| Contrast medium | 100.00% | 253.59 | 0.62 | 156.85 |
| **TOTAL** | | | | **1,003.36** |

Table 6. Pre-hospitalization, Analysis and tests costs (pre-procedure).

The average one-year follow-up cost per patient was €1,502.29, including drug treatment and diagnostic tests, emergency room visits and hospitalizations for different causes. Hospitalizations are a key point in calculating annual costs and cost-effectiveness analysis. In spite of the stents effectiveness in the treatment of coronary artery stenosis, these patients have many comorbidities and frequently visit the hospital. Although the drug treatment has the smallest weight on the total cost, it is also interesting to look at the evolution of drug treatment in the patients. At first, nearly 100% of the patients had antiplatelet therapy, and at one-year follow-up only 25% had al least one antiplatelet drug.

In conclusion, the total annual cost of a patient with coronary artery stenosis who is treated with Endeavor RESOLUTE® stent is €11,707.5 in Spain, where the cost of the procedure represents over 60%. The cost is similar to or slightly lower than that referred by other previously published studies on DES (Moreu et al., 2009). The higher initial cost of DES may be largely offset in the long term by reducing the number of hospitalizations and revascularizations, especially compared to other treatment alternatives, as it can be observed in several published cost-effectiveness analysis discussed below.

## 4. Economic evaluation studies on Drug Eluting Stents

Despite DES are more efficient reducing restenosis incidence, they have higher costs than conventional stents. This has opened a discussion around the use of DES. The arguments against have often focused on concerns that higher acquisition costs lead to a significant and unacceptable increase of healthcare costs. The arguments in favor are focused on the potential of DES to compensate their higher acquisition cost with the reduction of the number of repeat revascularizations and the costs associated with them (Macaya, 2004; Valdés, 2004).

Therefore, from this discussion several studies have come up comparing costs and cost-effectiveness of different alternatives (Table 9). The TAXUS I-IV series of clinical trials

| 30 day follow-up | | | | |
|---|---|---|---|---|
| | % patients | Average use | Unit costs | Total costs |
| Emergency room | 7.21% | 1.00 | 126.21 | 9.10 |
| Blood transfusion | 0.45% | 2.50 | 132.62 | 1.49 |
| No. hospitalizations | 2.70% | 1.00 | | |
| ICU | | 3.92 | 1479.10 | 156.57 |
| no ICU | | 4.58 | 723.83 | 89.66 |
| Hemodynamist | | 1.33 | 33.24 | 1.20 |
| Nursing | | 1.50 | 15.10 | 0.61 |
| **TOTAL (per patient) 258.63** | | | | |
| **6 month follow-up** | | | | |
| | % patients | Average use | Unit costs | Total costs |
| Emergency room | 10.25% | 1.24 | 126.21 | 16.10 |
| Blood transfusion | 0.23% | 1.00 | 132.62 | 0.30 |
| No. hospitalizations | 8.66% | 1.13 | | |
| ICU | | 0.61 | 1479.10 | 87.69 |
| no ICU | | 5.32 | 723.83 | 376.88 |
| Hemodynamist | | 1.41 | 33.24 | 4.59 |
| Nursing | | 1.55 | 15.10 | 2.29 |
| **TOTAL (per patient) 487.85** | | | | |
| **12 month follow-up** | | | | |
| | % patients | Average use | Unit costs | Total costs |
| Emergency room | 12.44% | 1.20 | 126.21 | 18.90 |
| Blood transfusion | 0.46% | 3.00 | 132.62 | 1.83 |
| No. hospitalizations | 6.98% | 1.06 | | |
| ICU | | 0.29 | 1479.10 | 31.92 |
| no ICU | | 5.81 | 723.83 | 312.38 |
| Hemodynamist | | 1.06 | 33.24 | 2.61 |
| Nursing | | 1.11 | 15.10 | 1.25 |
| **TOTAL (per patient) 368.88** | | | | |

Table 7. Emergency room and hospitalization costs.

| | Pre-procedure | Discharge | 30 days | 6 months | 12 months |
|---|---|---|---|---|---|
| Aspirin | 96.65% | 99.11% | 68.69% | 65.60% | 25.35% |
| Clopidogrel | 83.48% | 99.55% | 68.47% | 64.92% | 15.67% |
| Ticlopidine | 0.22% | 0.00% | 0.00% | 0.00% | 0.00% |

Table 8. Antiplatelet treatment.

evaluated the efficiency of the Taxus DES for percutaneous coronary intervention. Thus, the TAXUS-IV study, the first randomized trial of this series that incorporated a big pre-specified cohort of patients managed in accordance with routine clinical practice without the need of angiographic follow-up, demonstrated that the use of paclitaxel-eluting stents increases hospitalization costs in $2,028 at first, although it was partially offset at one year by a reduction in the follow-up cost of $1,456 on the DES arm (Bakhai A et al., 2006). In this way, the average cost at one year was $14,583 for DES versus $14,011 for BMS (p-value<0.001). Then, the cost-effectiveness ratio for paclitaxel-eluting stents was $4,678 for avoided revascularization and $47,798 for Quality Adjusted Life Year (QALY) gained (Bakhai A et al., 2006).

| Study | Type of evaluation and synthesis | Interventions | Study population | Country | Period of study |
|---|---|---|---|---|---|
| AETMIS, 2004 | Cost-utility analysis | DES (sirolimus and paclitaxel coated) versus BMS | Régie de l'Assurance Maladie du Québec (RAMQ) database, unselected patients. Repeat revascularisation risk with DES taken from meta-analysis of published trials | Canada | 6-13 months |
| Bagust et al., 2006 | Cost-utility analysis | DES (sirolimus and paclitaxel coated) versus BMS | Cardiothoracic Centre (CTC) Liverpool population, unselected patients. Subgroup characteristics determined from a meta-analysis of published trials and CTC database | UK | 1 year |
| Bakhai A et al., 2006 | Cost-effectiveness analysis and Cost-utility analysis | DES (paclitaxel coated) versus BMS | Patients undergoing percutaneous coronary revascularization: results from the TAXUS-IV Trial | USA | 1 year |
| Bischof M et al., 2009 | Cost-utility analysis | DES (sirolimus and paclitaxel coated) versus BMS | unselected patients with symptomatic ischaemic coronary artery disease | USA | 1+ year |
| Brophy JM et al., 2005 | Cost-effectiveness analysis | DES (sirolimus) versus BMS | Hypothetical cohort of patients undergoing PCI | Canada | 9 months |
| Brunner et al., 2007 | Cost-effectiveness analysis and Cost-utility analysis | DES (sirolimus and paclitaxel coated) versus BMS | 826 patients included in the BASKET study- 'real-world setting' | Switzerland | 18 months |
| Cohen, 2004 | Cost-effectiveness analysis and Cost-utility analysis | DES (sirolimus) versus BMS | 1,058 patients with plannned PCI of a single complex coronary artery stenosis (single native coronary artery). The lesion was de novo, 15-30 mm in length with a reference vessel diameter of 2.5-3.5 mm. SIRIUS trial | USA | 1 year |

| | | | | | |
|---|---|---|---|---|---|
| Eisenstein EL et al., 2009 | Cost-utility analysis | DES (zotarolimus) versus BMS | 1,197 patients included in the ENDEAVOR II study | USA | 4 years |
| Ekman M, 2006 | Cost-effectiveness analysis | DES (paclitaxel coated) versus BMS | Unselected patients | Sweden | 1 year & 2 years |
| Greenberg, 2004 | Cost-effectiveness analysis | DES (sirolimus) versus BMS | Unselected patients | USA | 2 years |
| Goeree R et al., 2009 | Cost-effectiveness analysis and Cost-utility analysis | DES (sirolimus and paclitaxel coated) versus BMS | All stent procedures in the province of Ontario between December 1, 2003, and March 31, 2005, with a minimum subject follow-up of 1 year. | Canada | 2 years |
| Gulizia et al., 2004 | Cost-effectiveness analysis | DES (sirolimus) versus BMS | Data obtained from literature and adapted to Sicilian population, using data form a survey conducted in seven local catheterisation laboratories | Italy | 1 year |
| Kaiser et al., 2005 | Cost-effectiveness analysis | DES (sirolimus and paclitaxel coated) versus BMS | 836 patients included in the BASKET study- 'real-world setting' | Switzerland | 6 months |
| Lord SJ et al., 2005 | Cost-effectiveness analysis and Cost-utility analysis | DES (sirolimus and paclitaxel coated) versus BMS | Unselected patients | Australia | 1 year |
| Mittman et al., 2005 | Cost-effectiveness analysis | DES (sirolimus and paclitaxel coated) versus BMS | Patients treated in the trials (SIRIUS, TAXUS) and Babapulle meta-analysis | Canada | 1 year |
| Moreu et al., 2009 | Cost-effectiveness analysis | DES (zotarolimus) versus BMS | Unselected patients, based on Endeavour trials | Spain | 5 years |
| Shrive et al., 2005 | Cost-utility analysis | DES (sirolimus) versus BMS | Unselected patients, based on Canadian database of 7,334 patients undergoing PCI between 1998 and 2000 | Canada | Patients' lifetime |
| Tarricone et al., 2004 | Cost-effectiveness analysis | DES (sirolimus) versus BMS | Patients suffering from stable or unstable angina, with de novo lesion(s). Case mix derived from unselected population of 1,809 patients | Italy | 1 year |
| Van Hout et al., 2005 | Cost-effectiveness analysis | DES (sirolimus) versus BMS | 238 patients with stable or unstable angina with planned PCI for single de novo coronary lesions. SIRIUS trial | The Netherlands | 1 year |

Table 9. DES Economic Evaluations

Although the TAXUS-IV study was carried out in U.S., it can be extrapolated to the Spanish level, because in demographic terms its inclusion criteria make this study representative of the conditions in Spain (Stone et al., 2004; Stone, 2004). In Spain, the average age of patients with a percutaneous coronary intervention is 63 years old, as opposed to 62.5 years old from TAXUS-IV study. The male proportion in the Spanish population with coronary disease is 74%, whereas in the TAXUS-IV study it was 72%. The proportion of diabetic people in the Spanish population who suffer from heart disease is nearly 25%, as opposed to 24.2% in the TAXUS-IV study.

Since the TAXUS clinical trials were not performed in Spain, the data from the mentioned TAXUS-IV study were used to estimate the economic impact of the implantation of this stent in a Spanish hospital (Russel et al., 2006). The relevant cost data related to hospitalized patients that were considered for this estimation were collected from the Spanish costs database. The cost of a percutaneous coronary intervention was calculated based on the cost of Taxus versus BMS and multiplying by 1.54, assuming a standard mean of 1.54 stents per intervention. For the number of revascularization patients treated, a mean of 370 patients was assumed given the big difference in the number of patients treated in the Spanish hospitals. Some hospitals treat less than 200 patients per year, whereas other hospitals treat more than 1,000 (López-Palop et al., 2004).

The analysis showed an expected cost at 12 months of €6,934 per patient for Taxus group and €6,756 for BMS group, i.e. 2.6% more than the Taxus group. Although the the cost for the Taxus group is higher due to higher costs of materials, 84% of this difference was compensated later with a lower probability of repeat revascularization. The cost for each repeat revascularization avoided with Taxus was estimated at €1,568. At 24 months, the cost difference decreased to 1.8% and the low probability of repeat revascularization compensated 91% of the increment in the initial cost of the procedure.

It is important to emphasize that this cost difference requires a specific analysis in the case of high risk revascularization patients. These patients include those who have small vessels, suffer long lesions and, specially, diabetic patients, who, as said, represent the 25% of the population with coronary disease. In their case, at 12 months the BMS cost is already 3% higher than the Taxus cost, and the percentage increases to 4.5% at 24 months.

The budget impact analysis was carried out considering two different settings. In the first setting, 90% of all patients of percutaneous coronary intervention receive Taxus instead of conventional stents, and 20% of patients who receive coronary surgery become Taxus patients. In this setting, the budget impact is 0.5% higher than in the base setting, although due to the reduction of surgery and reintervention, the capacity to treat patients in the surgery room increases in 8.5% with the same fixed costs and the same infrastructure.

The second setting considers the treatment of 90% of the high-risk patients, while those not included in this group are treated with conventional stents. In this case, the savings compared to the base setting is nearly 1% and the increment of the surgery room capacity was 5% (Russell et al., 2006).

The Cypher sirolimus-eluting stent was assessed after the SIRIUS clinical trial, which was carried out in 2004 in U.S. (Cohen et al., 2004). The patient characteristics were very similar to TAXUS-IV study, being the average age 62 years, 72.6% the average of male patients and

25% the proportion of diabetic patients. The economic analysis could be extrapolated to the Spanish market too, although this study has not been carried out yet in Spain.

The cost difference in initial treatment was $ 2,856 higher in the case of the Cypher stent. However, follow-up and reintervention costs were significantly lower in this case, becoming $ 2,571 lower than with conventional stents. The total costs at one year for Cypher were $ 309 higher than conventional stents (Cohen et al., 2004).

The cost-effectiveness study concluded that the cost-utility per QALY was $ 27,540, within the acceptable thresholds from the hospital perspective. In addition, in some cases of the study where the lesion was longer than 25 mm, 3 stents were used instead of two long lengths. This would have reduced the number of stents by intervention from 1.4 to 1.3, therefore, the costs per patient would have decreased about $ 136. This study, compared with the previous one showed no significant differences in the costs for treating high-risk patients (Cohen et al., 2004). The analysis indicated that DES was economically dominant in patients with long lesions in small vessels.

The Taxus stent has also been studied in Sweden by a decision model based on the revascularization rate, the resource use with its Swedish unit costs and the utilities based on the literature (Ekman M, 2006). From the public financing perspective, the average cost per patient treated at one year was €7,913 and €7,328 for Taxus stents and conventional stents respectively (Ekman M, 2006). The cost per repeat revascularization avoided was € 5,126 at one year and € 3,900 at 2 years. The results were more favorable in high risk patients: €47,791 per QALY and €838 per repeat revascularization avoided at 12 months. The budget impact was assessed too with 2 hypothetical scenarios and a baseline scenario. In the first scenario, 80% of high-risk patients were treated with DES instead of conventional stents, and the budget impact analysis increased 0.8%. In the second scenario, in addition to 80% of high-risk patients treated with DES instead of conventional stents, 20% of surgery patients with multivessel disease were treated with DES, and the budget impact analysis decreased 0.8%(Ekman M, 2006).

On the other hand, from the RAVEL study, Randomized Study with the sirolimus-eluting Bx Velocity balloon expandable stent in the Treatment of Patients with de novo native coronary artery lesions, it was demonstrated that the sirolimus DES generated an increase in the cost of the procedure of €1,284 per patient, although the net cost per year only resulted in an increase of €54 per patient (Van Hout et al., 2005).

After the TAXUS-IV, SIRIUS and RAVEL studies, it was necessary to carry out a study that compared Taxus and Cypher with each other and included an evaluation against conventional stents. This study was conducted in Switzerland in the state of Basel, and was named BASKET (Basel Kosten Effektivitäts Trial).

The BASKET study (Kaiser et al. 2005; Pfisterer et al., 2009) included more than 850 patients randomized into 3 similarly sized groups: those who received an uncoated stent, those who received Taxus and those who received Cypher. Thus, the study was planned and carried out in order to compare the increased cost-effectiveness of the three alternatives in patients with percutaneous coronary intervention.

At six months it was observed that the use of DES reduced the adverse cardiac events rate in a 44%, especially in terms of revascularization, myocardial infarction or acute coronary

syndrome. There were not significant differences in efficacy between the two DES (Kaiser et al., 2005). This behavior continued for three years (Pfisterer et al., 2009), time in which the BASKET study was reevaluated. After these years it was also observed that these differences were more pronounced in patients who received long stents, while those who received shorter stents had fewer differences in effectiveness between DES and uncoated stents.

Regarding the compared cost of the three options, at six months the initial higher cost of Taxus and Cypher could not be compensated, with a cost €1,702 higher than in the case of the conventional stents. After six months, due to the reduction of adverse events, this cost was finally €902 higher (Kaiser et al., 2005). The cost-effectiveness in preventing adverse cardiac events was €18,311 higher for DES, although this was reduced significantly in the subgroups of high risk patients such as diabetics, people over 65 years old, patients with more than a treated segment, and so on. The cost-utility ratio between DES versus standard stents was €73,283 per QALY using EQ-5D index, and €54,546 by visual analogue scale (Kaiser et al., 2005).

Also, at 18 months, a higher total cost was observed in patients with DES compared to BMS (€11,808 [SD 400] per patient with DES and €10,450 [SD 592] per patient with BMS, mean difference of €1,358 [SD717], $p < 0.0001$), due to the high cost of the stent shown in the study (Brunner-La Rocca et al., 2007). Therefore, the calculation of cost-effectiveness ratio was €64,732 per major adverse cardiac events avoided, and €40,467 per QALY gained. The stent cost, the number of events, and QALYs were the main causes for not reaching an acceptable cost-effectiveness ratio.

In patients at low risk, the probability that DES reached an Incremental Cost-Effectiveness of €10,000 or less to prevent major adverse cardiac events was 0.016, but was 0.874 in patients at high risk. In this way, it denotes the major differences between Incremental Cost-Effectiveness of patients at low risk and high risk. When the cost-utility ratio is assessed, a similar pattern can be observed, being low-risk patients 41% less effective and more expensive with a probability of being cost-effective of 0.11 (threshold below €40,000 per QALY) whereas in the case of high-risk patients 76% of patients were more effective and cheaper than BSM, being the probability of cost-effectiveness of 0.975.

In the study of Shrive FM et al. (2005), it was estimated a cost per QALY of 58,721 Canadian dollars using the sirolimus DES compared to conventional stents. In diabetic patients and patients older than 70 years old the use of DES is more cost-effective. In this way, other short-term Canadian study (9 months) found that the cost per repeat revascularization avoided was 23,067 Canadian dollars and that the most cost-effective strategy was the use of DES in high-risk populations (7,800 Canadian dollars) (Brophy et al., 2005). Delimiting the vision to a hospital perspective, the cost-effectiveness ratio for avoided revascularization showed values in a range from 12,527 to 29,048 Canadian dollars (AETMIS, 2004).

Many other economic evaluation studies have focused on the comparison of DES vs. BMS combining various types of DES. Thus in Australia, from a National Health System perspective, the incremental cost per repeat revascularization avoided was 3,750 Australian dollars with sirolimus and 6,100 Australian dollars with paclitaxel at 12 months (Lord SJ et al., 2005). On the other hand, the cost per QALY was 46,829 Australian

dollars and 76,467 Australian dollars with sirolimus and paclitaxel respectively. The authors concluded that limiting DES to patients at high risk may improve the cost-effectiveness (Lord SJ et al. 2005).

In UK, where a treatment is considered cost-effective below €42,000 or with a neutral cost at 12-month follow-up from a public financing perspective, DES were not cost-effective in comparison to BMS except for a selected group of patients (Bagust et al., 2006). In the same way, a Swiss study of Kaiser et al. showed a higher cost per patient for DES compared to BMS with an average of €10,544 against €9,639 from a health system financing perspective. Thus, the average cost difference between the 2 types of stents was €1,702 per patient, showing a cost per cardiac event avoided of €18,311 and a cost per QALY of €50,000 (Kaiser et al., 2005). Again, the subgroup analysis showed that DES were more cost-effective in high-risk patients (older than 65 with multivessel disease).

The latest studies, which assessed both Taxus and Cypher, indicated that in patients not selected previously DES are not cost-effective and they are becoming more cost-effective in high-risk patients (Bischof M et al., 2009 , Goeree R et al., 2009). In this way, the Bischof study, based on 17 randomized trials, showed that the cost of BMS was $25,460, the cost of sirolimus was $28,250 and $29,299 for paclitaxel (Bischof M et al., 2009). It all means that the probability of being cost-effective in the United States (threshold of $100,000 per QALY) was 8.3% and 2.8% for sirolimus and paclitaxel, respectively (Bischof M et al., 2009). For the Ontario study the differences in the revascularization rate were observed mainly in patients with two or more risk factors. Therefore, the cost per repeat revascularization and the cost per QALY were above the threshold (Goeree R et al., 2009).

The latest alternative of DES on the market was Endeavor, a zotarolimus coronary stent. Endeavor has demonstrated its effectiveness and safety with the Endeavor-I study and its benefits in the Endeavor-II study (Fajadet et al., 2007). The latter showed that Endeavor reduces the probability of suffering an adverse cardiac event from 14.4% to 7.3% and the restenosis rate was 35% for BMS and 13.2% for Endeavor.

With clinical data from the Endeavor II study (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions), Endeavor clinical and economic benefits were assessed in U.S compared to BMS (Eisenstein EL et al., 2009). The clinical data, the resource use and the follow-up of 1,197 patients were used (598 Endeavor vs. 599 BMS), applying the quality of life of secondary sources over 4 years of follow-up.

The use of Endeavor versus BMS at 4 years reduced the target vessel revascularization rate (10.4 vs. 21.5, P <0.001), but the analysis showed no significant differences regarding mortality or non-fatal myocardial infarction. Applying a discount of 3% no difference in QALYs was observed (1.093 vs. 1.090; p = 0.69), or the total health costs ($ 21,483 vs. $ 21,680, P = 0.78) (Eisenstein EL et al., 2009).

Using the data from the ENDEAVOR-II, Moreu et al. performed a Markov model with monthly cycles to compare the efficacy data of Endeavor with other therapeutic alternatives and draw an economic of the Spanish market. Data on resource use associated with the different options and the unit costs were obtained from local data and were validated by

experts. These costs were expressed in 2007 Euros with a time horizon of 5 years (Moreu et al., 2009).

This analysis showed that the cost per restenosis avoided by Endeavor was €6,851 at 1 year and €10,831 at 5 years, and costs for adverse cardiac event avoided were €7,003 and € 11,322 respectively. In this way, the lower incidence of complications with Endeavor compared to BMS resulted in an improvement of quality-adjusted survival of patients, which was progressive and strongly associated with the simulation period of the analysis, being almost 0 at 1 year. Thus, an increment of QALYs is perceived over time, since the values of cost per QALY gained is €132,877, €34,229 and €10,505 to 1, 2 and 5 years respectively (Moreu et al. 2009),

This study also included a comparison with other alternatives such as surgery, and showed that Endeavor is a less expensive option, with savings decreasing over the period of analysis.

Therefore, this study coincided with the cost-effectiveness analysis of the BASKET study, in which the higher costs of DES compared to conventional stents were mainly due to the higher initial cost of the procedure. The results at 2 years showed that these short-term higher costs are partially offset by further reductions in the incidence of complications and revascularization need. In addition, cost-effectiveness ratios also decrease with time (Moreu et al. 2009; Kaiser et al., 2005).

## 5. Discussion

The risk of repeat revascularizations using BMS is between 5% and 14% in the published registries, which is much lower than that observed in clinical trials (over 30%). Therefore, the absolute reduction of repeat revascularization with DES compared to BMS, or the marginal improvement of DES, is very limited in actual life. This leads to a higher cost combination for DES compared to BMS and low improvements in the quality of live by a low latitude, which make it more difficult to obtain favorable cost-effectiveness ratios to DES in all the countries.

In the recent years, there has been a growing interest in economic evaluation of health technologies, with a progressive increment of the number of articles in medical journals. Nevertheless, this increment does not translate into an increment in the quality of the studies, and the lack of methodological strength has been the general trend. This is because economic evaluation is relatively a new field (its use in the healthcare system began, with few exceptions, in the nineties when the health cost soared and new technologies with higher prices progressively appeared) which uses methods and concepts alien to medical knowledge and causes confusion in the terms use and the followed objectives.

The economic evaluation try to determine which technology is more efficient or, which is the same, what technology produces better health outcomes depending on the resources invested, once the costs, risks and benefits are identified, measured and compared.

The economic implications of the use of DES have lead to the proliferation of economic evaluation studies throughout the world. In short, in relation to the use of DES, it is widely

acknowledged that its cost is the true limiting factor; for example, in our area the price of DES is 60-80% higher than conventional stents. Although many studies concluded that DES may be cost effective in large subgroups of patients, under real conditions, the DES cost-effectiveness do not come out favorably compared to BMS (Neyt M et al. 2009; Hill RA et al. 2007; Kuukasjärvi P et al., 2007).

In the current global economic crisis, the presentation of studies with data from the actual clinical practice which demonstrate a reduction in the final costs with the DES use in the national health system is crucial to decision making and efficiency. Therefore, the stents are still one of the crosshairs of Health Technology Assessment bodies. Since 2006, 8 HTA have been published with a moderate to high quality, which showed different conclusions based on the published clinical evidence, especially in terms of mortality. Five of them reviewed the published economic evidence and concluded that DES are more effective in high-risk patients, despite the great disparity between studies and the great variance in the results and cost-effectiveness ratios.

In conclusion, in the last years a great effort has been made to improve the safety and efficacy of new coronary stents. However, studies with larger patient populations and a long-term follow-up are necessary to evaluate the effectiveness of the new stents and then show that DES are a cost-effective treatment, because they will remain an important part of treatment of PCI in the near future.

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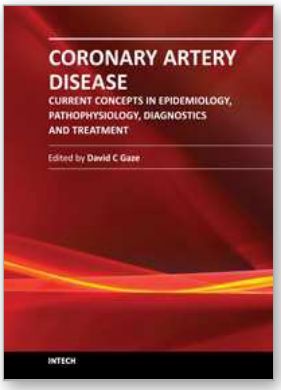


**Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment**

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Cardiovascular disease is ranked as the leading cause of death world wide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antiplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease



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