

# Empirical assessment of the impact of drug-eluting stents on the rate of use of coronary revascularization procedures

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**Objectives:** To assess the impact of the availability of drug-eluting stents (DES) in April 2002 in Emilia-Romagna (a four-million resident Italian region), on the rate of use of revascularization procedures. DES are expected to influence the rate of use of coronary artery bypass graft (CABG) and percutaneous coronary interventions (PCI). However, to date, little empirical information is available on the actual impact of this innovation on clinical practice.

**Methods:** A time series regression analysis of the monthly number of procedures (PCI and CABG) performed between January 1998 and March 2003.

**Results:** DES availability was associated with statistically significant changes in the use of revascularization procedures, although the size of the effect was always small or moderate. PCI increased only by 0.36 more procedures per month (approximately four per year), whereas more evident was the concurrent reduction of isolated CABG (4.15 fewer per month, that is fifty fewer per year). Overall, considering all the surgical revascularizations (i.e., CABG both isolated and associated with other interventions), there was a reduction of 2.52 procedures per month (thirty less per year).

**Conclusions:** Despite DES being at a very early stage of their diffusion process, our results indicate that they are already having an impact, although moderate, on the use of revascularization procedures. If these findings will be confirmed, they will have a substantial influence on the patterns of care for patients with coronary artery disease and relevant policy implications for health services.

**Keywords:** Patterns of care, Coronary artery bypass, Percutaneous coronary interventions, Drug-eluting stents, Time series analysis

Over the past decade, percutaneous coronary interventions (PCI) with endoluminal metallic stents became the procedure more frequently adopted in patients referred to coronary revascularization, over the more-invasive alternative represented by coronary artery bypass (CABG). Nevertheless, a rate of restenosis ranging from 20 to 40 percent within six months typically limits the clinical impact of this procedure (1;2).

Recently, a great deal of effort has been devoted to the development and testing of stents coated with drugs, aimed

at reducing the rate of restenosis through the inhibition of neointimal hyperplasia. Although the majority of these devices have been studied mainly on animals and on humans only in observational studies (1;2), results from the still few randomized clinical trials published to date appear highly promising. In particular, a double-blind randomized study showed a 0 percent incidence of restenosis for patients receiving a drug-eluting stent (DES) coated with sirolimus, as compared with 26.6 percent for those receiving uncoated stents (9). These findings are still waiting to be confirmed in further clinical evaluations, and their generalizability to less-selected populations of patients has to be verified.

One of the issues to be addressed is whether, and how, the availability of DES will influence the patterns of use of

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revascularization procedures. Although it has been anticipated that coated stents will decrease the volume of CABG procedures, reducing the number of patients requiring a surgical revascularization of a restenosis (8;13;14), others (5) pointed out that DES will change clinical indications for the primary treatment, with less patients referred for CABG for a de novo lesion.

In Emilia-Romagna, a 4-million resident Italian region, DES coated with sirolimus have been on the market since April 2002. In this study, we report a time series analysis aimed at exploring, a year after their appearance, whether DES are having any impact on the rate of use of revascularization procedures.

## MATERIALS AND METHODS

Information on the monthly number of CABG (isolated or associated with other surgical interventions) and PCI performed by the six cardiac surgery units and by the thirteen interventional cardiology centers in our region was retrieved from the regional database of hospital admissions. Data were available for the period January 1998 to March 2003, accounting for sixty-three monthly observations, fifty-two before and eleven after DES appeared on the market on April 2002. All the patients undergoing revascularization procedures at the regional centers were represented in the database.

The number of patients undergoing PCI with a DES inserted was retrieved from the Regional Registry of PCI, an initiative launched on July 2002 and aimed at providing information on the clinical characteristics of patients as well as on the type of intervention performed. Therefore, from July 2002, it was possible to monitor the degree of diffusion of DES in clinical practice.

It was anticipated that DES had, if any, a gradual rather than an abrupt effect on the number of revascularization procedures performed. Therefore, such an effect would have been detected in the form of a change in the trend of use of PCI and CABG (i.e., change in slope). The analysis was based on least square linear regression models adapted to the analysis of time series data (4) and adjusted for seasonality.

To assess the change in slope, the regression models included as covariates two dummy variables set up for the assessment of the trend before (fifty-one observations) and after (twelve observations) DES availability. In detail, set to zero, the time point at which DES were made available (April 2002), the first dummy (representing the slope before DES) was stepped backward and the second (slope after DES) stepped forward (8). The difference between before and after slope regression coefficients represents the change in slope attributed to DES.

Three regression models were used, with the monthly number of PCI, isolated CABG, and all CABG (isolated, plus those associated with other cardiac surgery procedures) as dependent variables, respectively. The values of the Durbin-Watson test (4), ranging between 1.8 and 2.1 for the three

models, suggested a low degree of autocorrelation of the data. The analyses were performed using SPSS for Windows version 9.0.1.

## RESULTS

The yearly and monthly numbers of revascularization procedures performed over the entire study period are outlined in Fig. 1. In the same figure, the proportion of PCI performed with the insertion of DES over the period July 2002 to March 2003, increasing from 5 percent in the first month to 21 percent in the last observation available, is reported.

Seasonally adjusted figures for PCI and CABG are described in Fig. 2. From inspection of the graphics, it was apparent that PCI had an escalating trend well before the introduction of DES, outnumbering CABG since early year 2000. In addition, trends in usage of the two procedures tended to diverge further over the last few months of the study period. Regression analysis confirmed this description (Table 1): DES availability was associated with a statistically significant change in slope, although of different sign and size for the two procedures.

For PCI, the change in slope attributed to DES was small (+0.36) although statistically significant, accounting for 4.32 more procedures performed over a twelve-month period after DES availability. Corresponding figures for surgical revascularization procedures were -4.18 (fifty fewer interventions per year) and -2.52 (thirty fewer interventions per year), respectively, for CABG isolated and associated with other cardiac surgery procedures.

## DISCUSSION

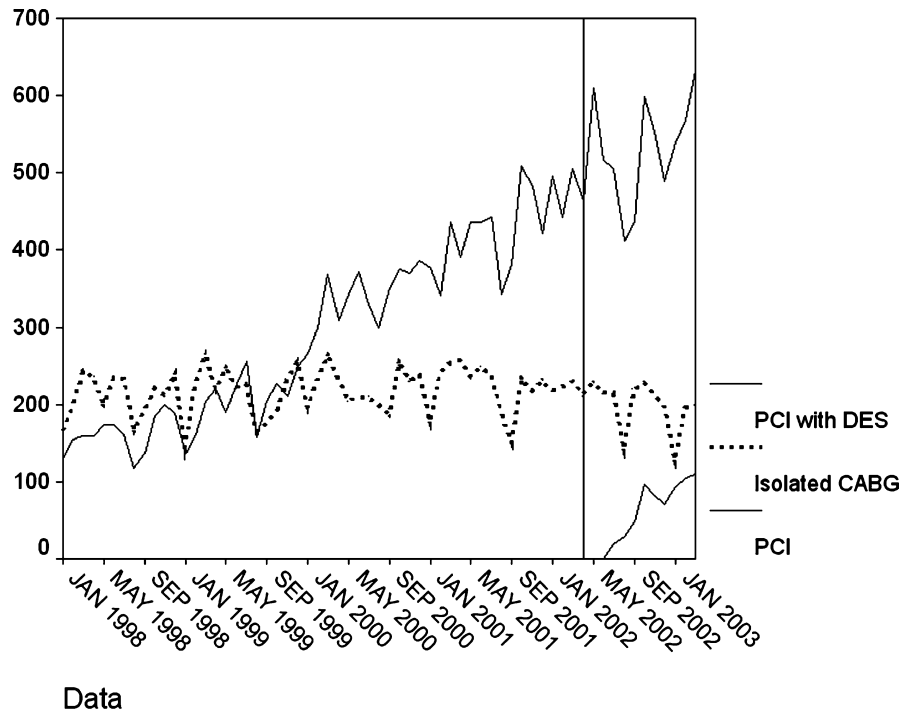
Adoption of new medical technologies poses a traditional challenge to health policy-makers because of (i) limited knowledge on their effectiveness, being the research information available (if any) usually drawn from highly selected

**Table 1.** Results of the Regression Models Assessing the Impact of DES on the Rate of Use of Revascularization Procedures in Emilia-Romagna (Italy)

Dependent variable	Covariates	Coefficients	<i>p</i> value
Number of PCI	Intercept <sup>a</sup>	486	<.001
	Slope before DES	7.46	<.001
	Slope after DES	7.70	<.001
Number of isolated CABG	Intercept <sup>a</sup>	226	<.001
	Slope before DES	0.29	.082
	Slope after DES	4.47	<.001
Number of all CABG	Intercept <sup>a</sup>	239	<.001
	Slope before DES	0.42	.024
	Slope after DES	2.94	<.001

<sup>a</sup> The value of the dependent variable at the time point when DES coated with sirolimus were made available (April 2002).

DES, drug-eluting stent; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.



	1998	1999	2000	2001	2002	First 3 months of 2003
<b>PCI</b>	1937	2444	4068	4994	6027	1740
<b>Isolated CABG</b>	2543	2570	2660	2675	2539	522

**Figure 1.** Monthly and yearly number of revascularization procedures performed in Emilia-Romagna (Italy). The vertical line indicates the time point at which DES coated with sirolimus were made available (April 2002). DES, drug-eluting stent; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

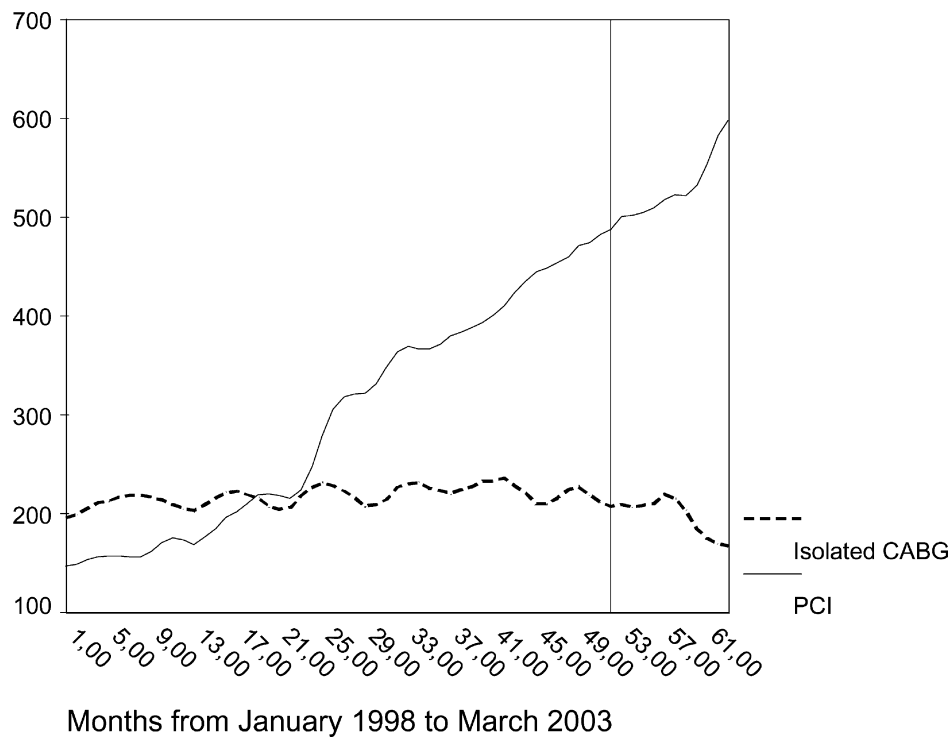
populations of patients included in randomized studies; (ii) short-term additional economic costs for the health-care system, and (iii) long-term impact on consumption profiles and organizational change in health services. DES are a case in point, and while further research is needed to confirm their effectiveness in less-selected populations of patients, diffusion in clinical practice is already intense, despite the unit cost being higher than the traditional stents.

To date, the impact of DES on clinical practice has been mostly the object of intensive speculation, supported by little empirical information, anticipating that, in the light of their potential major impact in reducing the risk of restenosis, they would have changed the indications to PCI and CABG, possibly increasing the number of patients referred for the former, rather than for the surgical intervention. To our best knowledge, this report is the first study providing some empirical evidence on the actual impact of DES on the patterns of use

of revascularization procedures. Others (5), relying on the opinions of experts, estimated that the proportion of patients who could be referred for PCI rather than for CABG due to the availability of DES is approximately 20 percent.

Indeed, our study confirms that DES have some impact on referral patterns, showing that, after their appearance on the market, there was a change in the usage trend for both the procedures. However, the size of the effect has been moderate so far, a very small increase in the number of PCI and a relatively more tangible reduction in CABG performed.

In interpreting these findings, one has to bear in mind that DES are just at the very beginning of their diffusion process in clinical practice. Although DES appeared on the market in April 2002, it took until the end of September 2002 before all the 13 regional centers had the device actually available. Overall, during the first twelve months from their appearance on the market, DES were used in 14 percent of



**Figure 2.** Patterns of use, adjusted for seasonality, of CABG and PCI in Emilia-Romagna (Italy). The vertical line indicates the time point at which drug-eluting stents coated with sirolimus were made available (April 2002). PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

patients undergoing PCI between July and December 2002, while this proportion raised to 21 percent over the first three months of 2003.

Among the factors limiting the adoption of this device in clinical practice, of special relevance is the economic burden on budgets for individual hospitals, a burden represented by the high unit cost of DES, as well as the relative uncertainty about the generalizability to routine clinical practice of the results observed in experimental settings. Specific policy initiatives were undertaken in our region to address both aspects. Under the aegis of the Regional Commission for Cardiology and Cardiac Surgery (an expert panel representing public and private regional centers of interventional cardiology and cardiac surgery), a regional registry of patients undergoing PCI was launched, prospectively collecting information on their clinical characteristics, outcomes, and type of stent used. Concurrently, centers were encouraged to prioritize the use of DES in patients with the highest risk of restenosis. To limit, at least in part, the economic impact of DES, an agreement was established with the manufacturer of sirolimus-coated stents. The manufacturer agreed to make DES available to all regional centers at a reduced unit cost, in return for access (within the limits of the protection of individual patient's privacy) to the clinical data of patients receiving their device.

Nevertheless, despite the moderate magnitude of the effect observed to date, these findings may still have relevant

implications on the long run. For instance, if the observed changes in trend remain stable, the reduction in the number of patients referred to CABG could make it difficult for surgical teams to maintain the minimum caseload required to assure good quality (7).

This study indeed has some limitations. First, our analysis is based on routine data collected for administrative purposes. The potential pitfalls of these approaches are indeed well known (11). In particular, in our context, the inherent limitations of the database prevented any opportunity for exploring the actual clinical indications in which revascularization procedures were used, and, therefore, for addressing the appropriateness of use of PCI and CABG (6;10). For the same reason, this study does not help in assessing whether the observed impact of DES on patterns of use of revascularization procedures is due to less patients referred to CABG for their primary treatment, rather than to a reduced number of patients experiencing restenosis after PCI. However, given the relatively short time frame after DES availability, the former explanation seems to be more plausible. Analyses are currently ongoing using information from the Emilia-Romagna Regional Registry of PCI to address those issues.

The design of the study, a time series regression analysis, also has some potential pitfalls. The possibility of correctly attributing the observed effect in trends of use of revascularization procedures to the factor at stake (DES appearance on the market) depends on the extent to which

the effect of other contextual factors can be reasonably excluded (3). However, nothing changed at the regional level in such a way as to influence the volume of CABG provided by the surgical centers, and the situation before and after the availability of DES was similar in terms of number of surgical teams and capacity of centers.

The reliability of time series analysis depends a great deal on the number of observations on which they are based (3;12). In our study, we could rely on a sufficiently large number of observations. However, we had only a relatively short time period (from April 2002 to March 2003) available for studying the post-DES phase. Nevertheless, there is sufficient consensus on the reliability of the statistical technique we used (a time series regression), even when dealing with relatively few observations (4;12).

## CONCLUSIONS

In conclusion, our findings support the view that the availability of DES is having some impact on the rate of use of revascularization procedures. DES effect is currently moderate, but already visible, mostly in terms of reduction in the volume of CABG performed. These results and their potential implications support the need for carefully monitoring the diffusion process of coated stents and their actual impact on clinical practice.

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