The impact of drug eluting stents availability on the treatment choice among medical therapy, percutaneous or surgical revascularisation and on 4-year clinical outcome in patients with coronary artery disease: a cohort study

Zoran Olivari,¹ Paolo Stritoni,¹ Claudio Burelli,¹ Domenico Scalia,¹ Stefano Brocco,² Ugo Fedeli,² Francesco Avossa,² Dario Ferlin,¹ Bernhard Reimers,³ Giuseppe Grassi,⁴ Alessandro Fontanelli,⁵ Carlo Valfrè¹

To cite: Olivari Z, Stritoni P, Burelli C, *et al*. The impact of drug eluting stents availability on the treatment choice among medical therapy, percutaneous or surgical revascularisation and on 4-year clinical outcome in patients with coronary artery disease: a cohort study. *BMJ Open* 2012;**2**:e001926. doi:10.1136/bmjopen-2012-001926

► Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-001926>).

Received 24 August 2012
Accepted 6 September 2012

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

For numbered affiliations see end of article

Correspondence to
Dr Zoran Olivari; zoran.olivari@gmail.com

ABSTRACT

Objective: To investigate the influence of the availability of drug eluting stents (DES) on treatment choice (TC) among medical therapy (MT), coronary by-pass surgery (CABG) or percutaneous coronary interventions (PCI) and the consequent clinical outcomes in patients hospitalised because of coronary artery disease (CAD).

Design: Observational study comparing two cohorts hospitalised immediately before, and 3 years after DES availability.

Setting: Thirteen hospitals with cardiology facilities.

Patients: 2131 consecutive patients with at least one coronary stenosis >50% at coronary angiography (CA) after exclusion of those with acute myocardial infarction or previous CABG or associated relevant valvular disease.

Main outcome measures: Treatment choice after CA and 4-year clinical outcomes.

Results: TC among MT (27% vs 29.2%), PCI (58.6% vs 55.5%) and CABG (14.5% vs 15.3%) was similar in the DES and bare metal stent (BMS) periods ($p = 0.51$). At least one DES was implanted in 57% of patients treated with PCI in 2005. After 4 years, no difference in mortality (13.8% vs 13.2%, $p = 0.72$), hospital admissions for myocardial infarction (6.6% vs 5.2%, $p = 0.26$), stroke (2.2% vs 1.7%, $p = 0.49$) and further revascularisations (22.3% vs 19.7%, $p = 0.25$) were observed in patients enrolled in the DES and BMS periods. Only in patients with Syntax score 23–32 a significant change of TC ($p = 0.0002$) occurred in the DES versus BMS period: MT in 17.4% vs 31%, PCI in 62.2% vs 35.8%, CABG in 20.3% vs 33.2%, with similar 4-year combined end-point of mortality, stroke, myocardial infarction and further revascularisations (45.3% vs 34.2%, $p = 0.087$).

Conclusions: Three years after DES availability, the TC in patients with CAD has not changed significantly as well as the 4-year incidence of death, myocardial

ARTICLE SUMMARY

Article focus

■ During the year 2002 drug eluting stents (DES) were introduced in clinical practice, however the impact of their availability on the treatment choices among medical therapy, percutaneous coronary interventions (PCI) or coronary by-pass surgery and the consequent clinical outcomes of real-world patients with coronary artery disease (CAD) is still unknown.

Key messages

■ Four years clinical outcome of consecutive patients with confirmed CAD in preDES and DES periods was similar; an increase of indications to PCI was observed only in subgroup of patients with Syntax score 23–32, which did not result in improved clinical outcome.

Strengths and limitations of this study

■ As far as we know, this is the first attempt to understand the impact of DES availability on the treatment choices in patients with CAD and consequent clinical outcomes up to 4 years. In future, it may be advisable to focus similar studies only to the subgroup of patients with higher Syntax scores.

infarction, stroke and further revascularisations. In subgroup with Syntax score 23–32, a significant increase of indications to PCI was observed in the DES period, without any improvement of the 4-year clinical outcome.

INTRODUCTION

Drug eluting stents (DES) have been available in clinical practice since 2002 in Europe

and 2003 in the USA, where they have been used in up to 90% of percutaneous coronary interventions (PCI) in the following years¹ because of their effectiveness in reducing the rate of restenosis when compared with bare metal stents (BMS).² This effect did not result in a reduction of mortality or myocardial infarction within 4 years after the intervention in randomised clinical trials.^{3–4} In observational studies, the results are somewhat conflicting: some confirmed that DES are effective in reducing the need for new revascularisation without affecting the rate of mortality or myocardial infarction^{5–7} whereas others reach contrasting conclusions, that is, DES would favour a reduction in mortality and myocardial infarction with minimal impact on the need for repeat revascularisation.⁸ In any case, only patients who actually had undergone PCI with DES or BMS were the object of all those studies.

Surprisingly, despite the cost concerns associated with the widespread use of DES,⁹ no data are available regarding the possible influence of DES availability on the choice between different therapeutic options in patients with confirmed coronary artery disease (CAD) and the consequent impact on the clinical outcomes of this population as a whole.

The aim of our study was to investigate whether the availability of DES had any effect on the choice of treatment among medical therapy (MT) versus PCI versus coronary by-pass surgery (CABG) in patients with confirmed CAD and to observe the impact on overall clinical outcomes up to 4 years.

METHODS

Consecutive patients admitted to participating hospitals for acute or stable ischaemic heart disease and in whom the presence of CAD was demonstrated with coronary angiography (CA) in the first quarter of 2002 (in Italy, DES became available in April 2002) were compared with a similar group in the first quarter of 2005, when DES were routinely used during PCI.

The study was approved by the ethics committees in all participating hospitals.

Participating hospitals

Thirteen hospitals with cardiological facilities in the Veneto Region participated to the study. In four of them both interventional facilities and cardiac surgery were available, in six only interventional facilities and in three there was no cath lab on site.

Patient selection and data collection

All consecutive patients resident in the Veneto Region, admitted in any of the participating hospitals during the two selected quarters (1 January 2002–31 March 2002 and 1 January 2005–31 March 2005), who underwent CA, with or without PCI, were identified from hospital discharge records, by means of ICD9CM procedures,

codes 88.55, 88.56, 88.57 and 36.0, in the presence of primary or secondary CAD-related diagnosis (410–414).

In hospitals without on-site cardiac surgery, all consecutive eligible patients were selected (sampling fraction=1), whereas, in order to limit the workload, in the four remaining hospitals with higher volumes of patients, 50% of the eligible patients were selected by means of random sampling (sampling fraction=0.5).

All hospitals provided complete clinical records as well as CA films for all selected patients, and these were analysed on site by a dedicated team of experts (Heart Team), including one clinical cardiologist (PS), one interventional cardiologist (CB), one cardiac surgeon (DS) and one expert in economics and health management (DF).

The exclusion criteria were intended to eliminate clinical and angiographic bias that could strongly influence the choice among MT, PCI or CABG: (1) absence of at least one coronary artery stenosis >50% on visual examination; (2) patients hospitalised because of ST segment elevation acute myocardial infarction (STEMI), who underwent CA with the aim of performing primary or rescue PCI (only stable patients with STEMI lasting more than 24 h were enrolled); (3) patients hospitalised because of scheduled staged PCI; (4) patients with previous CABG and (5) patients with associated valvular, congenital or aortic disease committed to cardiac surgery. Moreover, patients with unavailable hospital records were excluded.

All other patients, with at least one coronary artery stenosis >50%, were enrolled.

For each patient medical records were carefully analysed, films of coronary angiographies were reviewed, and the Syntax score¹⁰ was calculated. Based on the results of Syntax trial,¹¹ cut-off points at 22 and 32 scores were considered for the analysis. Data regarding the interventional and surgical procedures were obtained directly from the hospitals where the procedures had been performed.

From the regional archives of discharge records and mortality data, a 4-year follow-up was obtained for all patients enrolled. It included vital status, cause of death and hospitalisation for acute myocardial infarction, stroke or new revascularisation with PCI or CABG.

Statistical analysis

According to the study design, which involved a stratified sampling, the hospital sampling weights were applied to estimate the total number of patients treated at the participating centres. Bivariate and multivariate analyses, taking into account the sampling weights, were carried out with the statistical packages SAS V.9.1.3 and Stata V.11. Clinical presentation, type of treatment and outcomes of patients evaluated in 2002 and 2005 were compared by means of the Rao-Scott χ^2 (a Pearson χ^2 corrected for the study design). Differences in the overall survival between the two groups were assessed by the logrank test. OR, with 95% CI for the risk of death

at 4 years, were estimated by a multiple logistic regression model for survey data, including factors selected a priori: age, gender, year and type of treatment, variables included in the Clinical SYNTAX score (Syntax score, creatinine clearance and left ventricular (LV) ejection fraction (EF)), type of coronary syndrome, and presence of diabetes mellitus.

Initial patient identification, linkage with mortality and hospitalisation data and statistical analyses, were performed by the Epidemiological Department of the Veneto Region (SER).

RESULTS

A total of 2464 patients were sampled for the review of clinical and angiographic data; 970 had at least one exclusion criteria, therefore the final study population consisted of 1494 patients hospitalised for acute or stable CAD and at least one coronary artery with stenosis >50%: 676 in the BMS period and 818 in the DES period. By applying the hospital sampling weights, this stratified sample represented a study population of 2131 patients treated in the participating centres during the two periods (1003 subjects in 2002 and 1128 in 2005).

Demographic characteristics of the two groups are compared in table 1: patients enrolled after STEMI underwent a CA more than 24 h after symptom onset and were clinically stable. History of hypertension and previous PCI were more frequent in 2005. No difference was observed, between the two groups, with regards to clinical status at admission, LV EF and the severity of the coronary artery disease. In both periods, the majority of patients had one/two vessel disease or a Syntax score <23. Among patients treated with PCI, the procedure was performed for restenosis of previous PCI in 12.6% versus 9.0% ($p=0.125$) patients in 2005 and 2002, respectively.

The choice of treatment in the BMS and DES periods

The choice of treatment among MT, PCI or CABG was similar in 2005, when compared with 2002 (table 2), in both stable as well as unstable clinical conditions, with the majority of patients undergoing revascularisation. In patients treated with PCI, the overall use of stents significantly increased and in those sent to CABG the off-pump surgery significantly decreased in 2005 when compared with 2002. In the DES period, 376 patients (33.3% of the study population) received at least one DES.

The revascularisation was complete (no residual vessel >2 mm with stenosis >70% supplying viable myocardium) in 82.6% vs 79.0% ($p=0.22$) of patients treated with PCI and in 81.6% versus 76.1% ($p=0.33$) in those treated with CABG, in the BMS and DES period, respectively.

Prescriptions at discharge significantly increased in 2005 for all medications recommended as Class IA or IB in recent clinical guidelines.¹²

In table 3 the different therapeutic options are summarised for subsets of patients based on their Syntax

Table 1 Demographic, clinical and angiographic characteristics of the study population: percentages weighted to reflect 1003 subjects treated in 2002 and 1128 in 2005

	2002 (1003)	2005 (1128)	p Value
Male (%)	75.1	76.9	0.45
Age (mean)	65+10,7	66+11	0.071
Age by decades (%)			0.48
<45	3.4	2.7	
45–64	41.7	38.8	
65–74	33.6	34.0	
>75	21.3	24.4	
Diabetes mellitus (%)	31.9	28.8	0.22
Arterial hypertension (%)	68.5	73.6	0.04
Hypercholesterolemia (%)	75.1	75.8	0.76
Previous PCI (%)	23.0	28.5	0.03
Previous MI (>3 months)	29.2	28.3	0.52
Clinical status at hospital admission			0.24
STEMI (%)	6.8	8.2	
NSTEMI/unstable angina (%)	45.8	48.7	
Stable CAD	47.5	43.2	
LV EF (%)			0.13
<25	7.6	7.6	
35–50	21.6	17.2	
>50	70.8	75.2	
Number of vessels with ≥50% stenosis (%)			0.76
LM	7.9	8.3	
1	26.8	28.4	
2	30.3	31.4	
3	35.0	31.9	
Number of vessels with ≥70% stenosis (%)			0.48
LM	1.8	2.7	
1 vessel	41.4	40.9	
2 vessels	27.3	27.7	
3 vessels	22.0	19.3	
Syntax score (%)			0.17
<23	71.8	73.5	
23–32	18.7	15.2	
>32	9.5	11.3	

CA, coronary angiography; LM, left main coronary artery; LV EF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction (coronary angiography performed at least 24 hours after symptom onset).

score: only in patients with an 'intermediate' score, a significant increase in the use of PCI and a reduction of those sent to CABG or left in MT occurred during the DES period.

Four years clinical outcomes

The overall mortality during a 4-year follow-up (figure 1) was similar for patients enrolled in 2002 compared to those enrolled in 2005 (13.2% vs 13.8%, $p=0.72$); the same was confirmed for cardiovascular mortality (8.2% vs 8.1%, $p=0.94$).

Table 2 Treatments performed and discharge medications: percentages weighted to reflect 1003 subjects treated in 2002 and 1128 in 2005

	2002 (1003)	2005 (1128)	p Value
TC (all patients)			0.51
Medical therapy (%)	29.2	27.0	
PCI (%)	55.5	58.6	
CABG (%)	15.3	14.4	
TC (STEMI/NSTEMI/UA) (n)	527	641	0.45
Medical therapy (%)	23.3	19.7	
PCI (%)	63.2	66.6	
CABG (%)	13.5	13.7	
TC (Stable CAD) (n)	476	487	0.82
Medical therapy (%)	35.8	36.6	
PCI (%)	47.0	48.0	
CABG (%)	17.2	15.4	
PCI patients			
BMS and/or DES implantation (%)	84.6	93.6	<0.0001
Only BMS (%)	100	43.1	
Only DES (%)	—	46.9	
DES + BMS (%)	—	10.0	
Number stenosis treated (%)			0.17
1	56.9	58.4	
2	26.9	28.7	
≥3	16.2	12.9	
Number of implanted stents (%)			0.002
0	15.4	6.4	
1	54.5	58.6	
2	19.7	22.6	
≥3	10.4	12.5	
CABG patients			
EC during CABG			0.01
complete (%)	62.0	76.5	
partial (%)	0.7	3.3	
Off-pump (%)	37.2	20.3	
Graft type			0.25
Only arterial (%)	8.4	15.7	
Only venous (%)	7.0	6.3	
Arterial + venous (%)	84.6	78.0	
Medications at discharge (all patients)			
Aspirin	86.8	91.9	0.01
Thienopiridins	54.2	64.5	0.0001
Statins	57.6	68.7	<0.0001
ACEI or ARB	56.1	66.5	0.0001
Betablockers	69.5	77.0	0.002

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMS, bare metal stent; CABG, coronary artery by-pass surgery; CAD, coronary artery disease; DES, drug eluting stent; EC, extracorporeal circulation; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction (only when coronary angiography performed at least 24 hours after symptom onset); TC, choice of treatment; UA, unstable angina.

Hospital admissions for acute myocardial infarction and stroke were also similar between the two periods; further revascularisations occurred more frequently during the first year of follow-up in patients enrolled in

Table 3 Treatment choice in patients with different Syntax scores: percentages weighted to reflect 1003 subjects treated in 2002 and 1128 in 2005

	2002 (1003)	2005 (1128)	p Value
Syntax score <23 (number)	719	829	0.87
Medical therapy (%)	29.6	31.1	
PCI (%)	64.4	63.1	
CABG (%)	6.0	5.8	
Syntax score 23–32 (number)	187	172	0.0002
Medical therapy (%)	31.0	17.4	
PCI (%)	35.8	62.2	
CABG (%)	33.2	20.3	
Syntax score >32 (number)	95	127	0.15
Medical therapy (%)	23.2	12.6	
PCI (%)	28.4	24.4	
CABG (%)	48.4	63.0	

For the year 2002 in 2 patients the Syntax score could not be computed
CABG, coronary artery by-pass surgery; PCI, percutaneous coronary intervention.

the DES period, and became similar after the 4-year follow-up (table 4). The 4 years combined end-point of major cardiovascular events (death or acute myocardial infarction or stroke) occurred in 17.9% versus 19.3% (p=0.52) of patients enrolled in 2002 vs 2005, respectively.

In patients treated with PCI in 2002 vs 2005, the 4-year mortality was similar (9.2% vs 10.6%, p=0.52).

In patients treated with PCI in the DES period, no difference in mortality was observed at 4-year follow-up among those with at least one implanted DES if compared with patients without DES (9.1% vs 12.6%, p=0.25).

In patients with a Syntax score of 23–32, the subgroup in which a significant increase of PCI as choice of treatment was observed in 2005, a statistically insignificant trend toward increased mortality occurred after 4 years of follow-up in DES period compared with the BMS period (23.3% vs 16.0%, p=0.18); the same was observed for the combined end-point of mortality, stroke, myocardial infarction and further revascularisations (45.3% vs 34.2%, p=0.087).

Further revascularisations were performed more frequently with PCI (20.7% vs 16.1%, p=0.035) and less frequently with CABG (2.7% vs 4.8%, p=0.044) in patients enrolled in 2005, as compared with those enrolled in 2002.

At multivariate analysis (table 5), the independent determinants of increased 4-year mortality were older age, choice of MT, Syntax score >23, LV EF <50%, eGFR <30 ml/min, diabetes mellitus and STEMI at presentation, whereas no impact of the BMS or DES periods was detected. With regard to the combined end-point (mortality, myocardial infarction, stroke and further

Figure 1 Survival during 4-year follow-up of patients enrolled in 2002 and 2005; Log-Rank test=0.2236; p=0.6363.

revascularisations), the independent determinants of worse outcome were older age, choice of MT versus CABG, Syntax score >33, eGFR <30 ml/min, LV EF

<35%, diabetes mellitus and presentation with STEMI (table 6) with neutral impact of BMS or DES period.

DISCUSSION

Ideally, the introduction of a new treatment should answer the unmet needs of patients with a specific disease and, therefore, if really effective, it should have a measurable effect on the clinical outcomes or quality of life for the overall population of these patients.

In some fortunate historical moments, the availability of new technologies may immediately improve the clinical outcomes of a given population with a specific illness. There is no need for an RCT to demonstrate that the timely interruption of ventricular fibrillation with DC shock¹³ saves lives and improve the overall survival of patients with STEMI. Similarly, when a new treatment is really effective, even a small number of patients enrolled in a dedicated RCT may be enough: in patients with left main disease, CABG has demonstrated to improve survival, when compared with MT, after enrolling only 113 patients in an RCT.¹⁴ The role of RCTs is to compare the effectiveness of alternative treatment options, whereas, observational studies should assess interventions in real-world scenarios being frequently under-represented in RCTs. As above, when a new treatment is really effective, that is, the implementation of reperfusion strategies involving primary PCI in patients with STEMI, the impact on survival on the overall population of patients with STEMI may be much more evident in observational studies^{15 16} than in RCTs.¹⁷

With regards to DES, after the demonstration of their effectiveness in reducing the rate of restenosis² and, therefore, reducing the need for repeated

Table 4 Hospital admissions for myocardial infarction, stroke or further revascularizations during 4-year follow up and combined end-point with all-cause death: percentages weighted to reflect 1003 subjects treated in 2002 and 1128 in 2005

	2002	2005	p Value
Myocardial infarction (%)			
1 y	3.1	2.9	0.86
2 y	4.4	4.4	0.97
3 y	5.0	5.8	0.53
4 y	5.2	6.6	0.26
Stroke (%)			
1 y	0.5	1.2	0.18
2 y	0.9	1.5	0.31
3 y	1.4	1.7	0.67
4 y	1.7	2.2	0.49
Further revascularizations (PCI or CABG) (%)			
1 y	10.7	14.5	0.04
2 y	14.6	18.5	0.06
3 y	16.9	20.9	0.07
4 y	19.7	22.3	0.25
Death/MI/stroke/further revascularization (%)			
1 y	16.2	19.4	0.13
2 y	22.6	26.8	0.08
3 y	28.3	31.0	0.29
4 y	33.8	34.9	0.67

CABG, coronary artery by-pass surgery; PCI, percutaneous coronary intervention; y, year.

Table 5 Independent determinants of 4-year mortality. Odds Ratios (OR) with 95% Confidence Intervals (CI) and probability associated to a two-tailed test (p) estimated by a logistic regression model for survey data

	OR	95% CI	p Value
Age (years)	1.07	1.05 to 1.10	<0.001
Gender (female vs male)	0.67	0.42 to 1.07	0.093
Year 2005 vs 2002	0.98	0.68 to 1.41	0.918
PCI vs Medical therapy	0.45	0.30 to 0.69	<0.001
CABG vs Medical therapy	0.34	0.18 to 0.62	<0.001
Syntax score 23–32 vs <23	1.64	1.02 to 2.63	0.041
Syntax score ≥33 vs <23	2.15	1.19 to 3.89	0.011
eGFR 30–60 vs >60	1.44	0.91 to 2.26	0.119
eGFR <30 vs >60	4.70	2.06 to 10.07	<0.001
LV EF 35–50% vs >50%	2.05	1.36 to 3.08	0.001
LV EF <35% vs >50%	3.63	1.98 to 6.65	<0.001
Diabetes mellitus (yes vs no)	1.82	1.26 to 2.64	0.002
NSTEMI/UA vs stable CAD	1.42	0.94 to 2.13	0.093
STEMI vs stable CAD	2.15	1.08 to 4.30	0.030

CABG, coronary artery by-pass surgery; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate in ml/min; LV EF, left ventricular ejection fraction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; UA, unstable angina.

revascularisations, their utilisation in 2005 reached approximately 90% of interventional procedures in USA,¹ despite the demonstrated absence of an impact on other major cardiovascular events,^{3,4} and despite their cost-effectiveness could be demonstrated in a

Table 6 Independent determinants of 4-year combined end-point (mortality, myocardial infarction, stroke or further revascularizations). Odds Ratios (OR) with 95% Confidence Intervals (CI) and probability associated to a two-tailed test (p) estimated by a logistic regression model for survey data

	OR	95% CI	p Value
Age (years)	1.02	1.00 to 1.03	0.018
Gender (female vs male)	0.77	0.55 to 1.07	0.114
Year 2005 vs 2002	1.02	0.80 to 1.32	0.856
PCI vs Medical therapy	1.09	0.82 to 1.45	0.543
CABG vs Medical therapy	0.31	0.19 to 0.49	<0.001
Syntax score 23–32 vs <23	1.37	0.97 to 1.94	0.075
Syntax score ≥33 vs <23	2.07	1.32 to 3.27	0.002
eGFR 30–60 vs >60	1.32	0.94 to 1.86	0.112
eGFR <30 vs >60	4.66	2.15 to 10.07	<0.001
LV EF 35–50% vs >50%	1.28	0.94 to 1.74	0.120
LV EF <35% vs >50%	3.53	2.09 to 5.96	<0.001
Diabetes mellitus (yes vs no)	1.43	1.10 to 1.87	0.008
NSTEMI/UA vs stable CAD	1.20	0.91 to 1.56	0.191
STEMI vs stable CAD	2.08	1.30 to 3.33	0.002

CABG, coronary artery by-pass surgery; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate in ml/min; LV EF, left ventricular ejection fraction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; UA, unstable angina.

limited number of patients, that is, those at high risk for restenosis.^{9,18} Moreover, most recent guidelines on myocardial revascularisation, recommend DES implantation in all patients treated with PCI, in the absence of contraindications to extend double-antiplatelet treatment (Class I LOE A).¹⁹ This recommendation is based on a number of randomised, as well as observational studies published in the last 10 years, all of them addressing only the populations of patients who actually underwent revascularisation and comparing DES with BMS or CABG. We were not able to find any publication in Pubmed addressing the impact of DES availability on the overall population of patients with coronary artery disease in a real-world practice, candidates, therefore, not only for percutaneous or surgical revascularisation but also for MT, and were unable to understand whether the DES availability had any global impact on treatment options and, as such, on the clinical outcomes of this population. Consequently, the study questions were: (1) did DES availability push the indications towards percutaneous interventions and, if so, what was their overall impact on clinical outcome? To find an answer, our comparison was made by extracting upstream two groups of consecutive patients hospitalised in the BMS and DES periods for ischaemic heart disease in the presence of at least one stenosis ≥50% at CA. All patients with a strong clinical indication for PCI (STEMI in the first 24 h and those with previous CABG) or for surgery (associated conditions necessitating surgical correction) were excluded. The patients were enrolled in 13 hospitals with the aim of generalising the findings and the DES period was delayed until the first quarter of 2005 in order to compare a BMS period with a 'steady-state' DES period. The completeness of the enrolment of consecutive patients, together with the accurate review of all medical records and angiographies, represents one particular strength in our study and allows to overcome limits inherent in both the analyses limited at administrative records (lack of clinical data) and observational clinical studies (limited coverage and consecutivity concerns).

The main finding of our study is that the availability of DES, being actually implanted in one-third of patients observed in the DES period, had no impact on any of the major cardiovascular events during a 4-year follow-up, including the need for further revascularisation, in the overall population of patients hospitalised because of ischaemic heart disease and with at least one coronary artery stenosis ≥50%. In a multivariable analysis, the 4-year survival as well as the combined end-point of mortality, myocardial infarction, stroke and further revascularisations, were unaffected by the availability of DES, whereas older age, severe renal failure, LV EF reduction, higher Syntax score and the choice of MT, had an independent negative impact on survival.

It is not possible to compare our findings to other similar studies, since all published studies investigated patients who actually underwent revascularisation with

implantation of BMS or DES. The limitations of these observational studies were underscored by Yeh *et al*, suggesting that in order to assess the clinical impact of DES, the comparison of a BMS period versus a DES period could be more reliable than comparing patients implanted with one or the other type of stent, in spite of complex statistical analyses.²⁰ We took another step forward by taking into account all patients hospitalised because of ischaemic heart disease, and not only those who underwent revascularisation, in order to assess the overall clinical impact of DES availability, starting from the choice of initial treatment between MT or revascularisation with PCI or CABG.

Interestingly, our findings do not support the widespread belief that the availability of DES increased indications toward the PCI as the preferred treatment for patients with ischaemic heart disease; only in those with CAD of 'intermediate' complexity, that is, with a Syntax score of 23–32, we observed a significant increase of subjects undergoing PCI and a decrease of those left in MT or sent to CABG. This group represented only 17.6% of patients with demonstrated CAD and, therefore, any change of treatment options limited to this group will only marginally impact on the overall results on treatment choice. In our study, the shift toward the choice of PCI as the preferred treatment in this subgroup of patients did not impact on their clinical outcome.

Another finding of our study is that most of patients with demonstrated CAD showed a 'low' complexity disease, that is, Syntax score <23, therefore candidate to MT or PCI more easily than to CABG and with prognosis hardly to be influenced with any type of revascularisation.

As previously demonstrated in RCTs,^{3, 4} no significant difference in mortality or rate of myocardial infarction can be expected in patients treated with DES and this finding was confirmed in our study. With regards to our finding that even further revascularisations were not decreased in the DES period, the only hypothesis we can formulate is that the occurrence of clinical restenosis after PCI in a real-world population, during the BMS period immediately preceding the DES availability, was indeed not high: only 12% after 12 months in a series of 3146 consecutive patients.²¹ Even in the largest reported registry, accounting for 262 700 medicare patients, the use of DES had no impact on the further revascularisations when compared with BMS.⁸ Therefore, it may be difficult to demonstrate any meaningful difference in the need for further revascularisations associated with DES availability, observing the real-world population of patients with coronary artery disease as a whole.

Limitations of the study

The sample size was relatively small to reach statistical significance in some subgroup comparisons, for which the enrolment of a larger number of patients would have been required. On the other hand, if thousands and thousands of patients are to be enrolled to

demonstrate any effect of a treatment, it is very likely that the treatment itself has a limited clinical meaning.

Most of patients had 1–2 vessel disease and/or Syntax score <23 and therefore with expected favourable prognosis as demonstrated in a multivariable analysis. It seems reasonable that further investigation regarding the impact of DES on clinical outcome should address mainly the group of patients with higher Syntax score.

The follow-up was based on administrative data; therefore, we had no information on the quality of life of patients enrolled in the BMS and DES periods.

In our study, DES were implanted in 57% of patients who underwent PCI in 2005 and we are unable to extrapolate our findings to different scenarios, that is, the use of DES in 90% of the patients treated. In any case, the most recent data in Italy regarding 2010 show that at least one DES was implanted in 54.8% of 141 916 PCI procedures,²² supporting the fact that our data can be generalised to contemporary real-world practice.

CONCLUSION

In the Veneto Region, among patients hospitalised for coronary artery disease, confirmed by the presence of at least one coronary artery stenosis >50% at CA, the availability of DES did not change the proportion of those treated with MT or surgical and percutaneous revascularisation. Moreover, despite the fact that majority of the patients who received PCI in 2005 had at least one DES implanted, no effect on clinical outcome, including survival, rate of myocardial infarction, stroke and further revascularisations, was observed in the overall population when compared with the BMS period. Only in the Syntax score 23–32 subgroup, an increase of indications to PCI was observed in the DES period, without any improvement of 4-year clinical outcome.

Author affiliations

¹Cardiovascular Department, Cà Foncello Hospital, Treviso, Italy

²Epidemiological Department, Veneto Region, Padova, Italy

³Cardiovascular Department, Presidio Ospedaliero, Mirano, Italy

⁴Cardiovascular Department, Dell'Angelo Hospital, Mestre, Italy

⁵Cardiovascular Department, San Bortolo Hospital, Vicenza, Italy

Acknowledgements The authors wish to thank all participating centres for their valuable collaboration.

Contributors All the authors contributed to conception and design, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and approved the final version to be published.

Collaborators Mirano, 414 (B Reimers, A. Giacomini); Treviso, 362 (E. Franceschini, R. Canola); Mestre, 266, (S. Postorino, E. Polesel), Vicenza, 232 (F. Mistrorigo, L. Salvador); Conegliano, 191, (P. Delise, F. Caprioglio); Cittadella, 110, (M. Zanchetta, L. Pedon); Belluno, 108, (G. Catania, A. Bridda); S. Donà di Piave, 105, (L. Milani, F. D'Ambrosio); Venezia, 99 (G. Risica, M. Martini); Castelfranco Veneto, 71, (C. Cernetti, N. Pellizzari); Camposampiero, 70, (A. Zampiero, A. Di Marco); Feltre, 52, (M. Guarnerio, G. Scalchi); Montebelluna, 51 (G. Neri, F. Alitto).

Funding The project was supported by Regione Veneto Health Finalized Research n. 277/2007, DGRV n. 1510, 22/05/2007.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Epstein JA, Polsky D, Yang F, *et al.* Coronary revascularization trends in the United States: 2001-2008. *JAMA* 2011;305:1769-76.
2. Morice MC, Serruys PW, Sousa JE, *et al.*; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. *A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization.* *N Engl J Med.* 2002;346:1773-80.
3. Kirtane AJ, Gupta A, Iyengar S, *et al.* Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation.* 2009;119:3198-206.
4. Greenhalgh J, Hockenhull J, Rao N, *et al.* Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes. *Cochrane Database Syst Rev.* 2010;(5):pCD004587.
5. James SK, Stenestrand U, Linback J, *et al.* for the SCAAR study group. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. *N Engl J Med* 2009;360:1933-45.
6. Marzocchi A, Saia F, Piovaccari G, *et al.* Long-term safety and efficacy of drug-eluting stents: two-year results of the REAL (REgistro AngiopLastiche dell'Emilia Romagna) multicenter registry. *Circulation.* 2007;115:3181-8.
7. Malenka DJ, Kaplan AV, Lucas FL, *et al.* Outcomes following coronary stenting in the era of bare-metal vs the era of drug-eluting stents. *JAMA.* 2008;299:2868-76.
8. Douglas SP, Matthew Brennan JM, Anstrom JK, *et al.* Clinical Effectiveness of Coronary Stents in the Elderly: Results from 262,700 Medicare Patients in ACC-NCDR®. *J Am Coll Cardiol* 2009;53:p1629-1641.
9. Garg S, Eisenberg MJ. Drug-eluting stents: more dollars than sense? *JACC Cardiovasc Interv.* 2009;2:1188-9.
10. Sianos G, Morel MA, Kappetein AP, *et al.* The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1:219-27.
11. Serruys PW, Morice MC, Kappetein AP, *et al.* SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009 Mar 5;360(10):961-72.
12. Hamm CW, Bassand JP, Agewall S, *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2999-3054.
13. Lown B, Amarasingham R, Neuman J. New method for terminating cardiac arrhythmias. *Use of synchronized capacitor discharge.* *JAMA.* 1962;182:548-55.
14. Takaro T, Hultgren HN, Lipton MJ, *et al.* The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. *Subgroup with significant left main lesions.* *Circulation.* 1976;54(6 Suppl):III107-17.
15. Kalla K, Christ G, Karnik R, *et al.*, Vienna STEMI Registry Group. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). *Circulation.* 2006;113:2398-2405.
16. Saia F, Marrozzini C, Ortolani P, *et al.* Optimisation of therapeutic strategies for ST-segment elevation acute myocardial infarction: the impact of a territorial network on reperfusion therapy and mortality. *Heart* 2009;95:370-376.
17. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361:13-20.
18. Hill RA, Boland A, Dickson R, *et al.* Drug-eluting stents: a systematic review and economic evaluation. *Health Technol Assess.* 2007;11:iii, xi-221.
19. Wijns W, Kolh P, Danchin N, *et al.* Guidelines on myocardial revascularization. *Eur Heart J.* 2010;31:2501-55.
20. Yeh WR, Chandra M, McCulloch CE, *et al.* Accounting for the mortality benefit of drug-eluting stents in percutaneous coronary intervention: a comparison of methods in a retrospective cohort study. *BMC Medicine* 2011;9:78.
21. Agema WR, Monraats PS, Zwinderman AH, *et al.* Current PTCA practice and clinical outcomes in The Netherlands: the real world in the pre-drug-eluting stent era. *Eur Heart J.* 2004;25:1163-70.
22. www.ilgiornale.gise.it