Coronary artery stents:

a systematic review & economic evaluation

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Appraisal Committee Version

Addendum A

Data no longer confidential

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Review aims:

To assess the effectiveness and cost effectiveness of the use of coronary artery stents in patients with coronary artery disease (CAD).

Specifically the clinical review compares the use of:

- Stent versus Percutaneous Transluminal Coronary Angioplasty (PTCA)
- Stent versus Coronary Artery Bypass and Graft (CABG)
- Stent versus drug-eluting stent (DES).

The economic analysis compares the cost effectiveness of:

- Stent versus DES
- Stent versus CABG.

Report commissioned by: NHS R&D HTA Programme

On behalf of: The National Institute for Clinical Excellence

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Addendum 1

Drug-eluting stents: evaluation of clinical effectiveness including data confidential when report was submitted

Introduction

This Addendum includes data used in the evaluation of the clinical effectiveness of drug-eluting stents (Chapter 6) which were considered commercial in confidence when the report was submitted. These data have since been made public and therefore the relevant text in the results, discussion and conclusion sections (6.1, 6.2, 6.3) as well as outcome tables (Table 6H) and Figures 6A-E are presented with these data reinstated.

Readers should consult this Addendum when considering the Executive Summary, Chapter 6 and the Conclusions of the report.

6.1.3 DES: Data analysis

Meta-analysis is presented for event rate, mortality, AMI, and binary restenosis. Data are pooled using a fixed effect model with odds ratio and 95 percent confidence intervals. Where qualitative heterogeneity exists, a result of the application of a random effects analysis is also presented.

It is not within the remit of this review to compare stents eluting different pharmaceutical agents. However, within the presented analyses stents loaded with related compounds are labelled and grouped for ease of reference. Three studies (ASPECT, ELUTES and SCORE) evaluated the effects of differing doses of the same agent, while TAXUS II evaluated the effects of slow and moderate drug release. For the purposes of this analysis the results from these groups have been combined. Results of the analysis are presented in forest plots Figures 6A to 6E, while details are provided here.

DES: Event rate

Analysis of event rates favours DES at 6 (OR: 0.49, 95% CI 0.38 to 0.61) and 12 months (OR: 0.37, 95% CI 0.27 to 0.50). However, in the 6 month analysis there is heterogeneity, and the analysis was re-calculated using a random effects model. This more conservative analysis shifts the OR to 0.59 (95% CI 0.31 to 1.11).

The direction and significance of this is maintained in the two year RAVEL data (OR: 0.46, 95%CI 0.22 to 0.97)

DES: Mortality

Death in all studies was a rare event. There is no evidence of a difference between the groups. Event rates in the short-term do not differ between the groups. This trend is maintained in the RAVEL 2 year data. There are five non cardiac deaths in the DES arm of RAVEL to 2 years compared to one in the non DES arm, compared to one and two cardiac deaths in each respectively.

DES: AMI

There is no evidence of a difference in incidence of AMI between DES and stents in the short-term or at six months. Data at 12 months indicates an increase in AMI in the DES group. This outcome is predominated by the outcome of the SCORE trial. Two year RAVEL data show no difference between the groups in rate of AMI.

DES: Binary restenosis

Binary restenosis (greater than 50 percent) is reported for seven of the included studies at 6 months and at 9 months for PATENTCY, SIRIUS and E-SIRIUS. Analysing these data together suggests a benefit of DES over non-eluting stents in the taxane and sirolimus groups. This advantage is not evident in the evaluation of Actinomycin in the ACTION trial.

6.2 Discussion

Drug-eluting stents represent a simple adaptation of a currently provided technology. One of the attractions therefore is that if considered effective and subject to funding, it could be easily adopted. The vast majority of interventional cardiologists are enthusiastic about the use of drug-eluting stents. However, current available data has limited follow-up and it remains to be seen whether there will be greater frequency of late thrombosis or delayed restenosis; as

with all new technology it may be expected after the initial enthusiasm to have some drawbacks.

Not all cardiologists are enthusiasts: some point to evidence from preclinical animal studies that DES can cause significant medial necrosis and persistent local fibrin deposition, suggesting delayed healing. Animal studies have also shown a reduction in restenosis with DES at one month which is lost by six months, i.e. that the effects of the DES were temporary and probably only delayed healing. By comparison with animal models, the temporal response to healing is much delayed in man, and therefore some fear that short-term reductions in restenosis may not translate into long-term gains as late restenosis becomes more common.(175) Others point out that animal models differ depending on the species studied, and that these cannot be easily translated into human biology. We need therefore to consider the long-term human studies so far reported.

First in Man was an open non-comparative study in patients with coronary heart disease treated with a single sirolimus eluting velocity stent in Brazil and the Netherlands. Twelve month follow-up has been reported for the 45 patients,(176), showing no patient reaching more than 50 percent diameter stenosis at one year based on angiography. Neo-intimal hyperplasia, as assessed by intravascular ultrasound was found to be virtually absent both at 6 and 12 months. The authors conclude that the study demonstrates a sustained suppression of neo-intimal proliferation by the DES. Two year data has also been reported for the 15 patients from the Netherlands.(177) Within the following 2 years there were no additional events in these patients except that 2 had undergone significant lesion progression in a site remote from the sirolimus eluting stent and which required further intervention. Angiography showed no significant change in the stent minimal luminal diameter or percent diameter stenosis compared to earlier angiography. In general these studies are reassuring about the long-term safety of this DES. The 2 year data from RAVEL greatly increases the information available at two years, and is similarly reassuring about the long-term safety of this device. The results in revascularisations at two years are discussed below.

6.2.3 Comparability of interventions

[No confidential data used in Report.]

6.2.4 Outcomes

The trials reported to date repeat some of the problems identified in the comparison of stents to PTCA. They identify a variety of definitions of MACE or MACCE. Therefore, the difficulties of interpreting composite endpoints remain. There are problems identifying when revascularisations in particular were clinically or angiographically driven. A standardised definition of clinically driven revascularisations is now available and was applied in many of the studies reported here. However, the definition may mislead. For instance in the nine and twelve month results of SIRIUS, we are told that the revascularisation rate represents 'clinically driven' events only, but the definition of 'clinically driven' includes a purely angiographic criterion – 'a target lesion with an in-lesion diameter stenosis greater than 70 percent in the absence of the above mentioned ischaemic signs or symptoms'. It is argued that this criterion only identifies patients who would go on to have a clinically driven procedure within a short space of time anyway. However its effects on revascularisation rates are clearly seen in the RAVEL study, where a Kaplan-Meier plot (*Figure 2, page 1778* of the article) shows a clear increase in revascularisations at the time of the planned angiography. Some of this may have been because in patients with developing angina, the clinically driven intervention was delayed slightly in the knowledge that the patient was due to have an

angiography in the near future. Nevertheless, the results do suggest that the angiographic appearance had an effect on the revascularisation rate. The text describes patients either as having clinically indicated revascularisations but only in terms of angina or positive stress test, or in terms of purely angiographically driven revascularisations. It makes no clear distinction about whether any patients had revascularisation on the basis of greater than 70 percent restenosis alone. Communications with the sponsors suggests that no patients in fact had revascularisations for this indication only.

A point of note is the rate of revascularisation in the control arms of this and the SIRIUS study. The SIRIUS trial, in long lesions, reports broadly similar event rates in the control arm at 12 months (22.3 percent) to RAVEL at twelve months (22 percent in the control group) The PRESTO study is quoted in the BCIS submission,(178) as an example of likely revascularisation rates in clinical practice; it randomised 11,484 patients to either systemic immune suppression using Tranilast or to placebo before PTCA, which involved stenting in 83 percent of cases. The primary endpoint was death, myocardial infarction or ischemia-driven target vessel revascularisation: only a subgroup of 20 percent of patients had protocol driven angiograms. This combined event measure occurred in 15.8 percent in the placebo group and a similar number of the treated group at 12 months, and Tranilast was therefore unsuccessful.

This rate of events is substantially less than reported in the control arms of RAVEL or SIRIUS. This maybe an artefact, reflecting the patient selection for these trials with either relatively small (RAVEL) or small and long lesions both of which would carry a higher rate of restenosis than might have been seen in the less selected patients in PRESTO. It is claimed by the authors of the RAVEL(119) study that the higher restenosis rates in RAVEL was in keeping with a linear regression model derived from the BENESTENT(39) studies. But part of the difference might also lie in revascularisations being in part angiographically driven in RAVEL and SIRIUS.

In a PRESTO subgroup (about 20 percent of the total) studied by angiography, there was an association between restenosis and major adverse coronary events. In patients with no restenosis, 5 percent had MACE and 95 percent did not; in patients with restenosis 46 percent had MACE, 54 percent did not. This and other studies show a clear link between angiographic appearance and clinical event rates, although it is difficult to quantify this directly. The BCIS submission to NICE suggests approximately half of angiographically indicated revascularisations also being clinically indicated. However, in the nine month data from SIRIUS, the number of clinically driven TLRs is quoted as 4.1 percent in the DES arm and 16.6 percent in the non-DES arm and a rate of angiography driven revascularisations of 1.9 percent in the DES arm and 4.0 percent in the DES arm. So here we have between 70 percent and 80 percent of TLR 'clinically driven' as defined by the trial, rather than 50 percent typically suggested by cardiologists. Given the criteria for 'clinically driven revascularisations' in this study cited above, this high ratio of angiographic to clinically driven events seems artificial and probably no different to those in other studies.

The 2 year data from RAVEL provides further information on this aspect: there were no further angiographic follow-up in the 12-24 month period and so any further revascularisations may be more confidently attributed to clinical need. In the control arm, there were 16/118 clinically driven revascularisations by 12 months, and no further revascularisations by 24 months. In the DES arm, there was one clinically driven revascularisation by twelve months and a further 2 (total 3/120) by 24 months. The absolute

benefit is therefore 11.1% at two years. This suggests neither a major loss of effect of the DES due to delayed restenosis nor any additional benefit over the second twelve months. Longer-term follow-up is still desirable.

6.2.5 Subgroups of patients

Studies included in the review were not powered to assess effectiveness in subgroups of patients and therefore analysis of data by subgroup must be interpreted very cautiously. Key subgroups would be diabetics, patients with small vessels or long lesions, and LAD lesions.

Some preliminary results from SIRIUS have been reported to the review team in confidence: of the 1058 patients randomised, 279 had diabetes. For those people with diabetes, the TLR rates at 12 months were 8.4% in Sirolimus DES group versus 26.4% in the control group. MACE rates were 11.5% in Sirolimus DES group versus 29.1% in control the control group - a relative reduction by 60%, in keeping with the proportional reduction in the study as whole.

The RAVEL study also included a subgroup of diabetics but to date the only comment on outcomes in them is that the benefits seen overall were similar in diabetics and non-diabetics but whether this is in proportions of patients with restenosis or in the extent of restenosis is unclear. Some results from a diabetic subgroup in RAVEL are quoted in the BCIS submission to NICE, although a reference is not given nor are these data found in the publication to date.

Inclusion criteria for five of the included studies (ASPECT, ELUTES, RAVEL, SIRIUS and E-SIRIUS) indicated that they would include patients with vessel diameter less than 3.0 mm (small vessel). Presentation of the data did not allow for assessment of outcomes related to vessel size.

Other subgroups reported in SIRIUS, so far only in conferences, are those for lesions of the left anterior descending artery (LAD), another high-risk group. Here, the TLR on Sirolimus was 5.1 percent versus 19.7 percent in the control group, and the MACE rates were 8.5 percent on Sirolimus versus 22.5 percent on percent.

Patients experiencing AMI were excluded from studies of DES and therefore results cannot be generalised to this population.

So far therefore, data on subgroups is limited and should not be overstated. What limited data there is indicates that the relative benefits of drug-eluting stents are maintained in high-risk subgroups of diabetics and those with small vessels. Given the higher background risk of these patients, maintaining the proportionate benefits would lead to a greater absolute benefit and this may provide useful pointers in targeting DES. This is discussed in greater detail in Chapters 9 and 11 of this report.

6.2.6 Data availability

[No confidential data used in Report.]

6.3 Conclusions

The available data do not allow for any conclusions to be made with regard to the effect of drug-eluting stents on mortality or in the case of AMI.

Overall, the results indicate that the drug-eluting stents decrease rates of restenosis and therefore revascularisation following placement. The exact rate of lowering of

revascularisations seems to be by approximately 60 to 70 percent at 12 months, but there are difficulties in definitions of how many of these were clinically driven. Outcomes from one study indicate that this benefit is largely maintained over two years. However, we stress that these results are interim and incomplete, and we await definitive publication of studies confirming patient numbers and outcome.

Table 6H DES: Outcomes

Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
E-SIRIUS[E] *Formerly* CIC	Stent 177	9 months 22.6			*TVR* ***Free*** 9 months 76.9 TLR **Free** 9 months 78.3			*8 months:* 65/154 42.2
	DES 175	9 months 8.0			*TVR* ***Free*** 9 months 76.9 TLR **Free** 9 months 95.9			*8 months:* 6/151 4.0
RAVEL[E]	**Stent** **118**	1 year 28.8	In Hosp 0.0 1 year 1.7	In Hospital 2.5 1 year 4.2	*TVR (not TL)* 1year 1.7 TLR (all) 1year 23.7	In Hosp 0.0 1year 0.8	TLR 1 year 22.9	6 months 26.6 (In stent, n unclear)
	DES **120**	1 year 5.8	In Hosp 0.0 1 year 1.7	In Hospital 2.5 1 year 3.3	*TVR (not TL)* 1year 0.8 TLR (all) 1year 0.8	In Hosp 0.0 1 year 0.8	TLR 1 year 0.0	6 months 0.0 (In stent, n unclear)
RAVEL[G] *Formerly* CIC	**Stent** **118**	2 years 19.5	2 years 2.5	1 year [F] (7/118) 5.9 2 years 5.1	*TVR (not TL)* 2 years 2.5 TLR (all) 2 years 13.6	2 years 0.0	TLR 2 years 13.6	6 months 28/107 26.6
	DES **120**	2 years 10.0	2 years 5.0	1 year [F] (4/120) 3.3 2 years 4.2	*TVR (not TL)* 2 years 0.8 TLR (all) 2 years 2.5	2 years 0.8	TLR 2 years 1.7	6 months 0/105 0.0

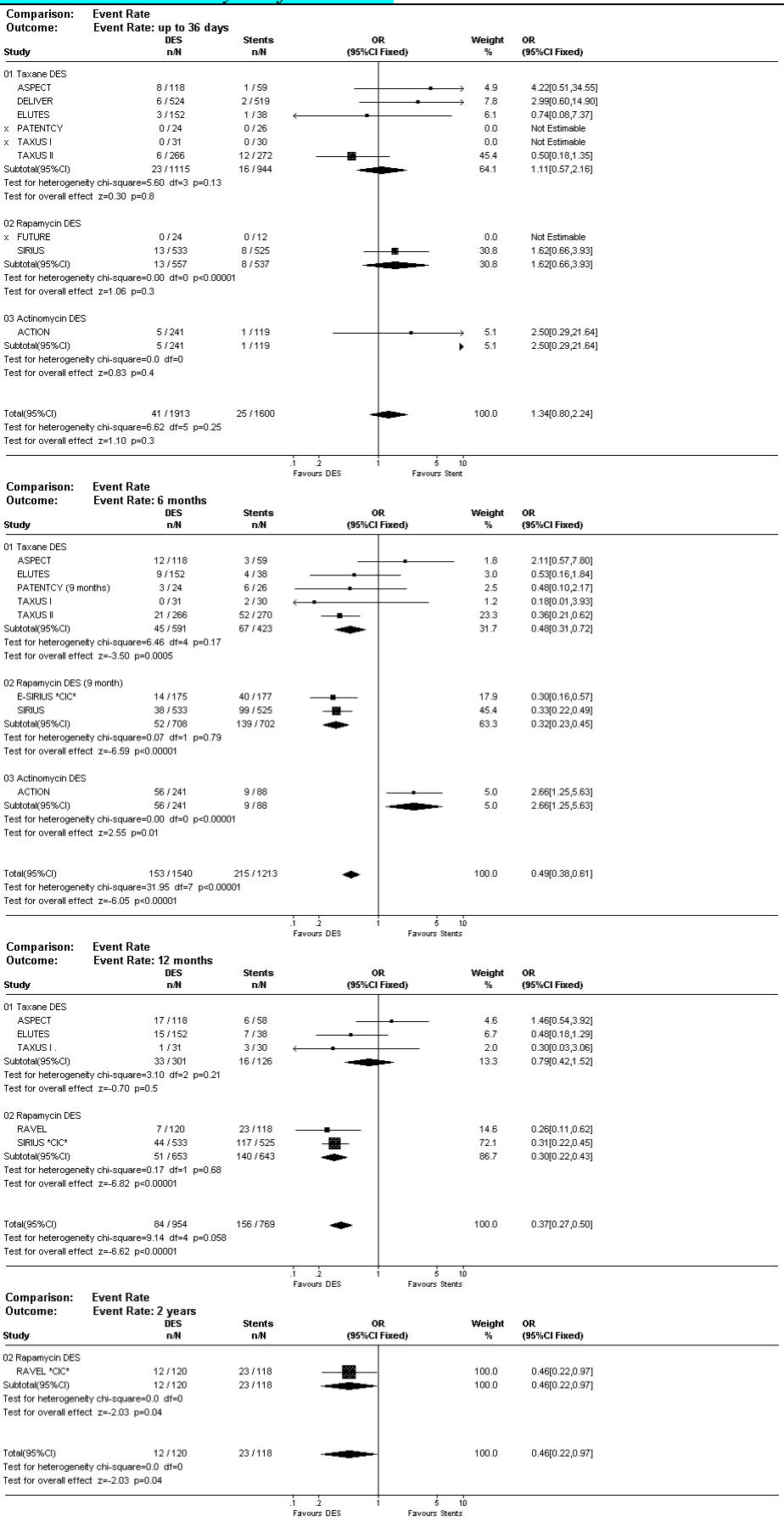
Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
SIRIUS	**Stent 525**	In hospital 1.5 9 months 18.9	In hospital 0.0 9 months 0.6	In hospital 1.5 9 months 3.2	*TVR (non-TL)* In-hospital 0.0 9 month 4.8 TLR: 30 day 0.0 9 month 16.6	30 days 0% blinded data	30 days 0% blinded data	*8 month In-segment:* 36.3 *8 month In-stent:* 35.4 *(n=353)*
	DES 533	In hospital 2.4 9 months 7.1	In hospital 0.2 9 months 0.9	In hospital 2.3 9 months 2.8	*TVR (non-TL)* In-hospital 0.0 9 month 3.2 TLR: 30 day 0.2 9 months 4.1			*8 month In-segment*: 8.9 *8 month In-stent:* 3.2 *(n=348)*
SIRIUS *Formerly* CIC	**Stent 525**	1 year 22.3	1 year 0.8	1 year 3.4	*TVR (non-TLR)* 1 year 6.7 TLR 1 year 20.0	9 mo CABG (Target Lesion) 8/525 TVR+TLR 1 year 3.0	9mo PTCA (Target lesion): 83/525 TVR+TLR 1 year 24.8	
	DES 533	1 year 8.3	1 year 1.3	1 year 3.0	*TVR (non-TLR)* 1 year 3.6 TLR 1 year 4.9	9 mo CABG (Target Lesion) 3/533 TVR+TLR 1 year 1.5	9mo PTCA (Target lesion): 20/533 TVR+TLR 1 year 7.5	

Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
TAXUS I(118) [B]	**Stent** **30**	30 days 0.0 6 months 6.6 12 month 10.0	30 days 0.0 12 months 0.0	12 months 0.0	30 day 0.0 TLR 6 month 6.6 1 year 10.0 TVR-non TLR 1 year 0.0	6 months 3.0 12 months 3.0	TLR (PCI) 6 months 6.6 6 months 10 Non-TLR (PCI) 1 year 0.0 1 year 0	6 months (n=29)10.3
	DES **31 (30)**	30 days 0.0 6 months 0.0 12 months 3	30 days 0.0 12 months 0.0	12 months 0.0	30 day 0.0 TLR 6 month 0.0 1 year (n=30) 0.0 TVR-non TLR 1 year (n=30) 3.0	6 months 0 12 months 0	TLR (PCI) 6 months 0 1 year 0 Non-TLR (PCI) 6 months 3 1 year 3	6 months (n=30) 0.0
TAXUS I *Formerly* CIC (Confidential information indicates denominator)	**Stent**				TLR 6 months St 2/30 TLR 1 year 3/30 TVR (non-TLR) 1 year 0/30	1 year 1/30		
	DES				TLR 6 months 0/31 TLR 1 year 0/31 TVR (non-TLR) 1 year 1/31	1 year 0/31		

Study name	Intervention	Event Rate (%)	Mortality (%)	Any MI (%)	Revascularisation (%)	CABG (%)	PCI (%)	BBR (%)
TAXUS II	**Stent 270**	30 day (n=272) 4.4 6 month 19.3	6 month 0.4	6 month 5.2	TVR 6 month 13.0 TLR: 6 month 15.5	6 month 0.7		*Stented segment:* 6 months 19.0 (n=263)
	DES 266	30 day 2.3 6 month 7.9	6 month 0.0	6 month 1.9	TVR: 6 month 6.8 TLR 6 month 3.7	6 month 0.7		*Stented segment:* 6 months 3.5 (n=256) Slow-DES: 2.3 (n=128) Mod-DES 4.7 (n=128)
TAXUS II- *Formerly* CIC	**Stent**	30d: 12/270 6mo: 52/263	6mo 0.6	6mo (Q and non Q) St comb 14/263, DES comb 5/259	6mo: TVR: 42/263 6mo TLR 35/263	6mo: St comb 2/263,		*Analysis segment:* 6 months 22.0 (n=264)
	DES	30d: 6/266 6mo 21/259	6 mo 0.0		6mo: TVR 8/259 6mo TLR: 10/259	6 mo: DES comb 2/259		*Analysis segment:* 6 months 7.0 (n=256) Slow-DES: 5.5 (n=128) Mod-DES 8.6 (n=128)

B TAXUS I TLR one person had PTCA then CABG at 198 days, E: combined clinically driven and angiographically driven data, as presented in (119); F: Data for MI as reported in Submission to NICE, G Only clinically driven events are reported

Figure 6A DES: Meta-analysis of event rate



CIC Information *formerly* Commercial in Confidence. RAVEL 12 month event rate data are clinically driven.

Figure 6B DES: Meta-analysis of mortality

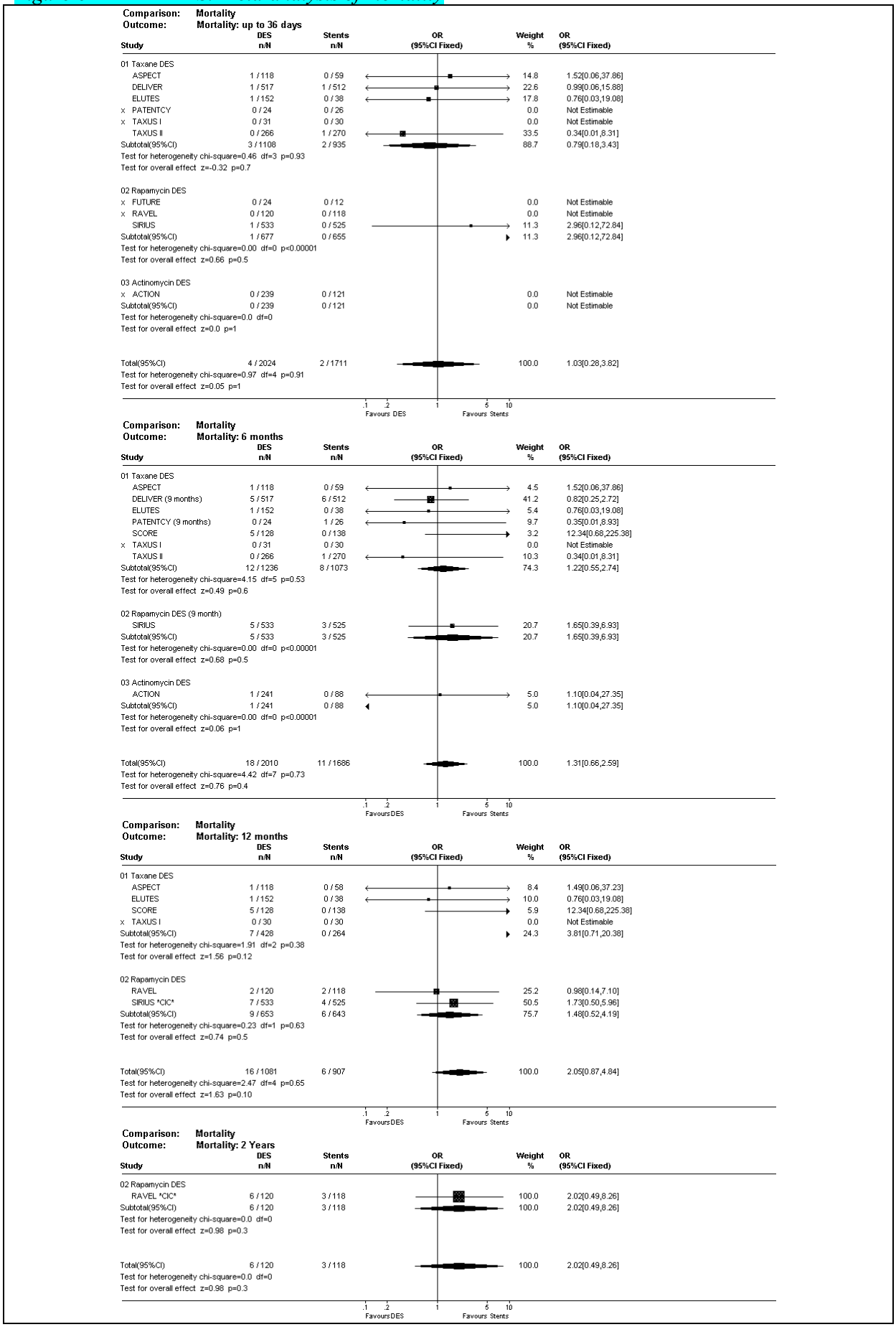


Figure 6C DES: Meta-analysis of any myocardial infarction

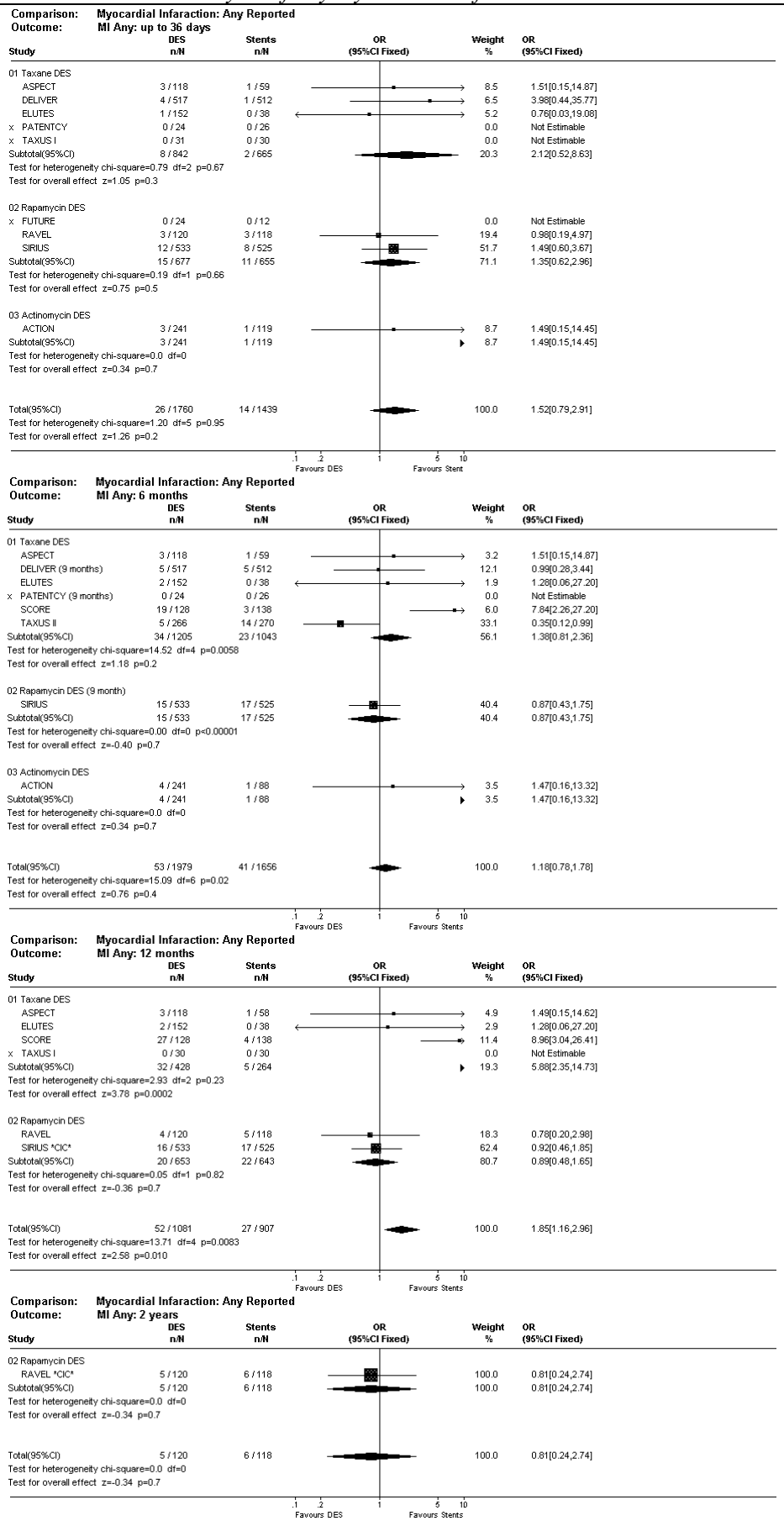
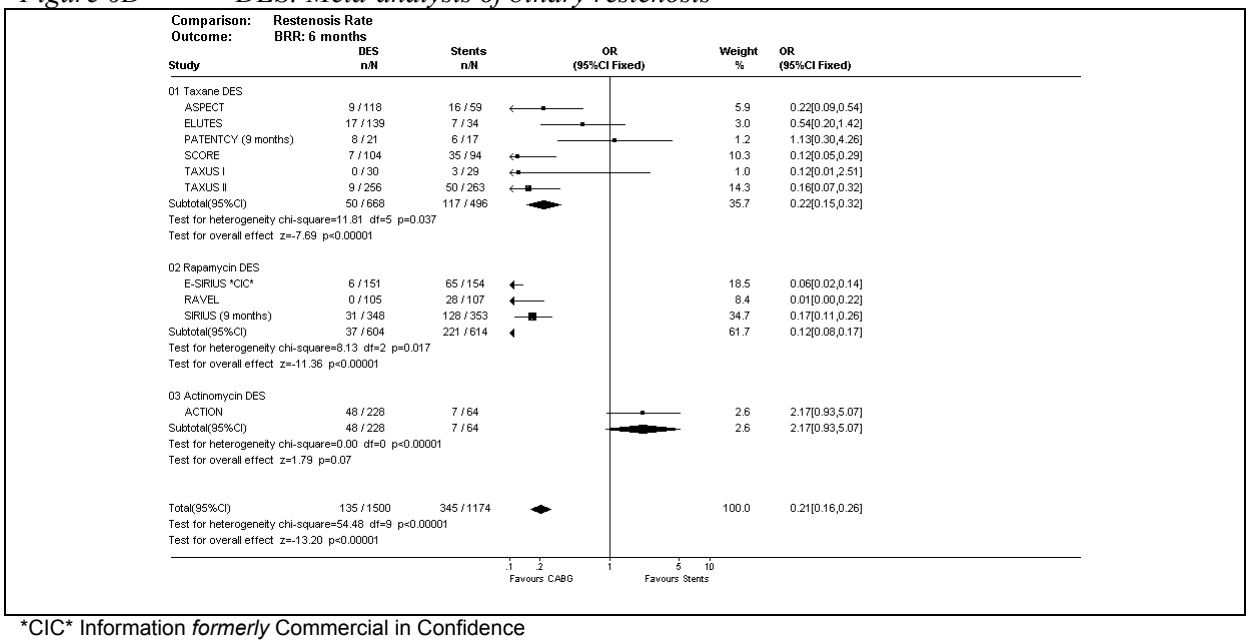
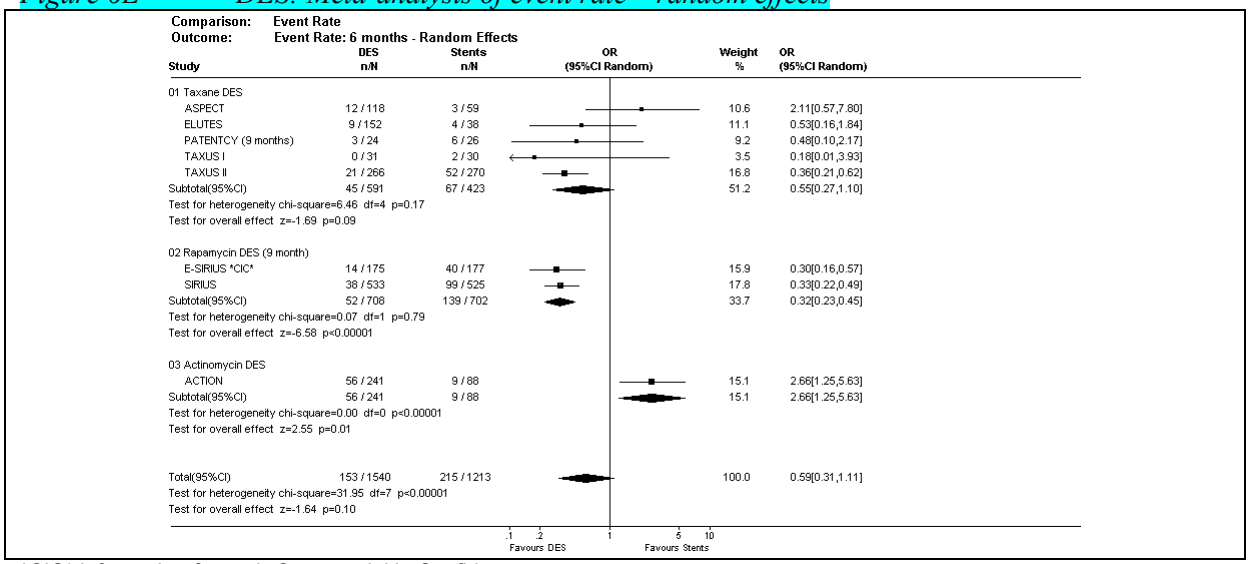


Figure 6D DES: Meta-analysis of binary restenosis



CIC Information *formerly* Commercial in Confidence

Figure 6E DES: Meta-analysis of event rate – random effects



CIC Information *formerly* Commercial in Confidence