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9th May, 2007.

Dear Reetan,

Medtronic response to Assessment Report Addenda 3'' and 4': Coronary Artery Stents for the Treatment of Ischaemic Heart Disease (Update to Guidance No. 71).

Thank you for the opportunity to comment on the addendas to the Assessment report. Whilst we appreciate that some minor amendments have been made to the economic model following requests/recommendations made by the Appraisal Committee and the cross industry working group since the appraisal committee meeting and industry response, we believe there to be some significant outstanding issues.

We would like to address our concerns around three key areas:

1. Responsiveness of the LRiG group to requests for reanalyses/data selection
2. New data available to the group since the original submission deadline (July 2005)
3. The impact of the new data on the cost-effectiveness of Drug Eluting Stents (DES)

1. Responsiveness of the LRiG group to requests for reanalyses/data selection

Appendix 1 tabulates the NICE project specification table provided to the LRiG group regarding further work to be undertaken on the original assessment report economic evaluation. The table has been annotated with comments from Medtronic re actions taken by LRiG to address the appraisal committee's concerns.

For example, it is perverse, that despite direct requests for LRiG to use data to assess risk factors for repeat revascularisation from alternative sources, LRiG have failed to do so and have continued to rely on single centre CTC audit data. Similarly, whilst Medtronic appreciate the incorporation of diabetes in the model as an independent risk factor, continued reliance on the CTC data to derive diabetes risk factors is unacceptable, as it is not representative of repeat revascularisation rates and underpowered to detect a difference in revascularisation rates between diabetics and non-diabetics. Furthermore, Table A6.2 *"Summary of risk model factors in reviewed papers"* does not present the results of a further 7 risk models, 5 of which identify diabetes as an independent risk factor for repeat revascularisation. These are but two examples (please refer to Appendix 1 for full listing) where it appears the wishes of both the appraisal committee and industry have been blatantly disregarded with no rationale given for LRiGs decisions.

We strongly believe that from the outset, the LRiG have been unable to make rational decisions due to a conflict of interest. Medtronic would like to refer to their letter of 7th June 2005 written to Professor Sir Michael Rawlins to express concern regarding the believed conflict of interest of the Liverpool assessment group. As outlined, two members of the assessment group (Professor Bagust and Professor Walley) published an article prior to the deadline for submission to this review which concluded that the technology could not be considered cost effective. We did not believe, and continue not to believe that members of the Liverpool group can be impartial under

these circumstances. The LRiGs continued insistence that their approach is correct despite it conflicting with the clinical and economic findings of other published literature on DES calls into question the fairness of this appraisal.

In the Code of Practice for Declaring and Dealing with Conflicts of Interest Issue published in April 2007 section 3.5 states:

3.5 **A personal non-pecuniary interest** in a topic under consideration might include, but is not limited to:

i) a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

ii) a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

It is clear that the Institute, rightly understand the need for such a code and that should this code have been in existence at the beginning of this appraisal LRiG could not have been selected as the assessment group for this appraisal as their publication record can clearly be interpreted "as prejudicial to an objective interpretation of the evidence". We ask, that in the interests of fairness, this point is raised at the next appraisal committee meeting as a matter of priority in addition to a discussion on the potential role of the DSU in this appraisal.

2. New data available to the group since the original submission deadline (July 2005)

As you are aware, due to significant delays in this guidance review, almost two years have passed since industry have been able to submit any new available data to the Institute for inclusion in the appraisal. Further to the letter received by the Institute on 12 March 2007 where we were incorrectly informed that Medtronic would have the opportunity to submit additional data to the Institute, Medtronic prepared a brief summary of new data available which we believe should be drawn to the attention of the appraisal committee (please refer to appendix 2). Whilst we realise that this will not be formally included into the assessment report we would like some key messages to be conveyed to the committee:

The Endeavor clinical program continues to generate strong cumulative evidence regarding Endeavor's overall performance, with consistent and predictable patient outcomes sustained over time. ***Indeed, the growing volume of positive data and number of patients with long-term follow-up continues to demonstrate the deliverability, the clinical efficacy and the strong safety profile of the Endeavor drug-eluting stent.***

The two-year results from the Endeavor III (EIII) trial confirms the positive clinical profile of the Endeavor drug-eluting coronary stent and bring to nearly 1,300 the number of Endeavor patients who have at least two years of follow-up. In EIII, at two years, the rate of Major Adverse Cardiac Events - a composite safety measure of death, repeat procedures and myocardial infarction (MI) – is 9.3% for Endeavor and 11.6% for the Cypher stent (p = 0.47). There is no statistically significant difference in the need for repeat procedures, or Target Lesion Revascularization (7.0% and 4.5% for Endeavor and Cypher, respectively, p = 0.50), or all-cause mortality (1.6% for Endeavor and 4.5% for Cypher, p = 0.14**). *However, fewer patients experienced heart attacks (MI) when treated with the Endeavor stent (0.6% vs. 3.6% for Cypher, p = 0.04) and the combined rate of heart attack and death also is statistically significantly lower among patients randomised to the Endeavor stent (2.2% vs. 7.1% for Cypher, p = 0.013).***

The reported pooled safety and efficacy data at one year on more than 1,300 patients from the Endeavor I, II, and III trials (including Endeavor II Continued Access) also confirms ***Endeavor's excellent safety record, with no observations of late stent thrombosis (more than 30 days after implant), and an overall thrombosis rate of just 0.3%. It demonstrates no significant***

differences in TLR or late loss across high risk subgroup parameters, such as vessel diameter size, lesion length and patient diabetic status.

The 3-year data from the 100-patient first-in-man Endeavor I (EI) clinical study, and the 2-year results from the 1,200-patient, double-blind randomised Endeavor II (EII) pivotal trial, with a patient follow-up for both trials of 97%, show low rates of restenosis and an excellent safety profile.

At 36 months, the combined rate for myocardial infarction, death and TLR in the EI study is 6%, while the 24-month MACE rate in EII is 10%. In EII, 93.5 percent of the Endeavor patients remain free of repeat procedures after two years, with a TLR rate of only 6.5 percent. In addition, in the ***EII study, there is no difference in mortality between the Endeavor (2.1%) arm and the Medtronic Driver (2.2%) bare metal stent arm, and the study also shows a 47 percent reduction in MACE between Endeavor arm (10.0%) and the Driver arm (18.7%).***

As a final point, Endeavor is safe by any definition, when using either the definition of stent thrombosis used by the clinical trial HRCI CEC , or re-adjudicated expanded ARC stent thrombosis definition, or even simply the composite rate of death and Q-wave MI. Concerning the ARC reclassification and in terms of cumulative incidence out to three years, proportionally more events were added in the bare metal stent groups than in the Endeavor DES groups; the difference in event rates was significant (1.0% vs 3.3%; P = 0.01). The overall increase is driven mostly by increased late and very late 'possible' events, with definite or probable events similar to prior reports using protocol definitions and trending lower for the DES arm.

The update on the safety data is especially pertinent to the Endeavor stent in this appraisal. In your communication of 11th April 2007, you stated that with respect to the economic modelling "Following the recent concerns over the safety of DES these sensitivity analyses have been extended to examine how the difference in the duration of clopidogrel use between BMS and DES may affect the cost effectiveness (see attached, Addendum 4'). This reflects recommendations made by the American Heart Association and the British Cardiovascular Intervention Society, that the duration of use of anti-platelet therapy (aspirin and clopidogrel) should be extended in patients who have received a DES to at least 12 months, and in particular in those patients whose lesions are thought to be high risk". What the Institute failed to mention was that the FDA and BCIS recommendations were made on the basis of three studies (Camenzind, Nordmann and Wenaweser) none of which include Endeavor related safety data.

In Medtronic's current IFU, it states that "In clinical trials of the ENDEAVOR stent, clopidogrel or ticlopidine was administered pre-procedure and for a period of at least 12 weeks post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis".

In view of this shorter duration of clopidogrel usage, the lack of data to show safety concerns associated with the Endeavor DES and the FDA statement that "The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy", may we strongly suggest that sensitivity analysis is conducted at a range of clopidogrel administration doses.

3. The impact of the new data on the cost-effectiveness of Drug Eluting Stents (DES)

In view of the new information available on the long-term efficacy and safety of Endeavor stent, we have re-analysed the cost-effectiveness model comparing the Endeavor stent to the Driver stent which was also included in the original submission (please refer to appendix 3). The model used the same inputs and assumptions as LRiG's model with the exception of using TVRs instead of total revascularisation rates and a longer time-horizon. Instead of extrapolating the

observed 9-month outcomes from the Endeavor II trial to one year and then assuming that no difference exists between Endeavor and Driver between years 2 and 5, the up-dated model now relies on observed trial outcomes at 24 months pooled from the Endeavor II and Endeavor III trials. All other model inputs and assumptions remained the same. The trial evidence of sustained effectiveness had a favourable impact on the cost-effectiveness of the Endeavor stent versus the Driver stent with an incremental cost-effectiveness ratio below £10,000/QALY gained at 5 years. The results were also confirmed in a probabilistic analysis which showed Endeavor to have a 76% and 86% probability of being cost-effective compared to Driver, using a £20,000/QALY and a £30,000/QALY threshold, respectively.

In summary, we have significant outstanding concerns regarding the actions of the LRiG in this appraisal. These concerns were raised early in the process and have been consistently relayed to the Institute. Since our manufacturers submission there has been a significant increase in the availability of both clinical and safety data on Endeavor which translates into a strong cost-effectiveness argument for the use of this product in the NHS. We submit this response alongside the cross-industry response from BCIA with which, in the main, we are in concurrence. With respect to section 4.1 of the BCIA response, we kindly request that you also refer to section two of the Medtronic response regarding the duration of clopidogrel administration.

If you have any queries, please fell free to contact me.

Best regards,

Elaine Oliver
Head of Health Economics and Market Access
Medtronic Ltd.

Appendix 1

NICE project specification with location of assessment group further analyses

Specification summary	Details of specification (with reference to location of further analyses within this Addendum)	Medtronic comments
Synopsis of the technical issue	At the Appraisal Committee meeting to discuss the development of the Appraisal Consultation Document a number of issues with the economic evaluation were raised. Most notably:	
	• The Appraisal Committee was aware that no statistically significant differences for mortality or morbidity were found in the trials for DES versus BMS, however the Committee was mindful that although the trial data showed no statistical significance, there was a difference in AMI in favour of DES and that this should be taken account of in the economic evaluation. The Committee was also mindful of data in the literature regarding mortality and morbidity of CABG and repeat angiography.	• The section "Are AMI and Mortality rates reduced by PCI/Stents?" (page 20) is not relevant to the comparison of BMS and DES. • Only AMIs occurring in the community are taken into account, the impact of in-hospital AMIs on utility are disregarded.
	• After reviewing the utility values in the Assessment Group's model the Committee was mindful of the possibility that there could be an additional disutility associated with CABG during the initial six weeks following the procedure compared with PCI.	• Instead of considering the <u>additional</u> disutility of CABG vs PCI, the new analyses decreased the disutility associated with PCI by 50% with reducing the recuperation time to two weeks compared to the original values. Furthermore, all utility calculations are based on assumed length of time required to restore utility to the base value (which was measured 60 days post-procedure, not two or four weeks post-procedure) with no endorsement even from a few experts.
	• The Committee was persuaded that neither the Liverpool (CTC) and the Leicester registry data or the randomised controlled trial data were representative of repeat revascularisation rates in patients and as the	• LRiG failed to use the data from the suggested sources, and made unjustified adjustments: o Failed to use the SCRR data, because Table 5.1 reports 84% & 89% stent

Specification summary	Details of specification (with reference to location of further analyses within this Addendum)	Medtronic comments
	BASKET trial and the Scottish Registry data had used methods that were likely to collect follow-up data from all patients, these data would therefore be more representative. • The Committee heard that there was no consensus in the trials or registries regarding which risk factors would put an individual at a high risk of revascularisation. They were persuaded that the Assessment Group's risk factors used in the current assessment report, based on the CTC registry data were one possibility, however risk factors which had been used in the previous appraisal should also be included in the current model. The Committee also heard that diabetes should be considered as an independent risk factor for restenosis too. • The Committee discussed the significance of the price premium (difference between DES and BMS price) and were mindful of the possibility that the price premium used in the Assessment Group's model was possibly too high (£560), given the procurement deals that took place in certain areas that brought the price premium down to less than £300. As a result of these points, further work was requested to be undertaken.	usage rate, but data is only in line with the rated used by LRiG with an assumed 60% stent usage rate o Conversion of rates to 12 month outcomes: adoption of smaller than documented multiplier without specific evidence to support it • Continued reliance on the CTC data to derive diabetes risk factors is unacceptable, as it is not representative of repeat revascularisation rates and underpowered to detect a difference in revascularisation rates between diabetics and non-diabetics. Furthermore, Table A6.2 *"Summary of risk model factors in reviewed papers"* does not present the results of a further 7 risk models, 5 of which identify diabetes as an independent risk factor for repeat revascularisation.
How will these questions be addressed in an addendum?	The Assessment Group will be asked to: • identify data in the literature regarding mortality and morbidity of CABG and repeat revascularisation. • identify additional utility values in the first six weeks following CABG or PCI.	• Used assumptions only

Specification summary	Details of specification (with reference to location of further analyses within this Addendum)	Medtronic comments
	• identify the parameter values for the base-case scenario accordingly using data from the Scottish registry for absolute risks, relative risks for the two sub-groups (small vessels and long lesions) from the trial data, additional utility values and price premium. • identify from the literature and review whether diabetes is an independent risk factor for restensosis. • develop a model, containing these new parameters with an appropriate time horizon, for example 12 months • synthesise the available information and calculate the degree of uncertainty around the cost effectiveness estimate using sensitivity analysis.	• The data from the Scottish Registry was not used; 6-month data was used for the relative risk reduction of the two sub-groups, which seriously underestimates DES effectiveness • The review was not complete and omitted papers which did actually show diabetes to be an independent risk factor • Results are presented for the "assumed" average number of stents with no source or justification provided
Relevant new evidence requested	• Data in literature regarding mortality and morbidity of CABG and angiography • Data on absolute risk of revascularisation from the Scottish registry data • Clinical evidence regarding whether diabetes is an independent risk factor for restenosis.	

Specification text taken (unedited) from: http://www.nice.org.uk/page.aspx?o=293164

Appendix 3

Update to the cost-effectiveness model of the Medtronic AVE ABT-578 coated Driver coronary stent (Endeavor®) vs the bare metal Driver® stent in *de novo* native coronary artery lesions

1.1. Methods

The same methods were used as in the original submission of evidence with the exception of the length of follow-up available from the clinical trial programme. At the time of development of the model, the Endeavor II trial [Fajadet et al., 2006] reported all outcomes of interest at 30 days and 9 months past the index procedure. Results up to 24 months are now available from Endeavor II and also from Endeavor III [Kandzari et al., 2006], a prospective, randomised trial comparing the Endeavor stent to the Cypher Sirolimus-Eluting Coronary Stent System.

Efficacy variables for the Driver stent were taken directly from Endeavor II, while efficacy variables for Endeavor were pooled from the Endeavor II and Endeavor III trials. The 30 day results were used directly in the model, while the 24 month probabilities (conditional upon not having the event in the first 30 days), were converted to monthly cycle probabilities. The model extrapolates up to five years based on the BENESTENT I trial [Kiemeneij et al., 2001]. It was assumed that there is no difference between the Endeavor and the Driver stent after the second year.

Table 1.1 Updated model parameters

	ENDEAVOR II			ENDEAVOR III			POOLED		
	%	event	n	%	event	n	%	event	n
30 day outcomes with Driver									
Death	0.0%	0	594						
AMI	3.5%	21	594						
TVR	1.2%	7	594						
30 day outcomes with Endeavor									
Death	0.2%	1	595	0.0%	0	323	0.1%	1	918
AMI	2.7%	16	595	0.6%	2	323	2.0%	18	918
TVR	1.2%	7	595	0.0%	0	323	0.8%	7	918
2-year outcomes with Driver									
Death	2.2%	13	578						
AMI	4.0%	23	578						
TVR	16.6%	96	578						
2-year outcomes with Endeavor									
Death	2.1%	12	582	1.6%	5	323	1.9%	17	905
AMI	2.9%	17	582	0.6%	2	323	2.1%	19	905
TVR	8.4%	49	582	15.3%	48	313	10.8%	97	895

The base-case model assumed no difference between the two stents after the second year. In an alternative scenario Endeavor was assumed to have continued better performance compared to Driver. A meta-analysis of randomised trials compared BMS and stents eluting sirolimus or paclitaxel [Babapulle et al., 2004]. The odds ratios calculated from the pooled trials were used to model Endeavor's performance in years 3-5.

1.2. Results

1.2.1. Base-case results

Model predictions for clinical outcomes were comparable to actual observations in the clinical trials (see Table 1.2).

Table 0.2 Comparison of predicted clinical outcomes with source trials

	Model prediction: Endeavor	**Endeavor II observation: Endeavor**	**Model prediction: Driver**	**Endeavor II observation: Driver**
At 30 days				
No MACE*	97.21%	97.17%	95.29%	96.30%
TVR	0.76%	0.76%	1.18%	1.18%
AMI	1.96%	1.96%	3.54%	3.54%
Death**	0.56%	0.11%	0.88%	0.00%
At 24 months				
No MACE*	86.30%	85.30%	79.06%	77.16%
TVR	11.24%	10.84%	17.61%	16.61%
AMI	2.10%	2.10%	3.97%	3.98%
Death**	1.72%	1.88%	2.42%	2.25%
	Model prediction: Endeavor		**Model prediction: Driver**	**Benestent I observation: BMS**
At 5 years				
No MACE	78.06%		71.51%	65.63%
TVR	14.10%		20.45%	19.53%
AMI	6.66%		8.50%	8.59%
Death	5.19%		5.87%	5.86%
CVA	0.38%		0.38%	0.39%

* MACE in model includes death, AMI and TVR, while MACE in Endeavor II trial included death, AMI, emergent CABG and TLR

** The model assumes that a certain proportion of AMIs and CVAs will always be fatal

Base-case deterministic model results are shown in Table 1.3. Although the price premium of Endeavor is above £500, Endeavor was only slightly more costly at five years than Driver due mainly to the reduced need for revascularisations in the first year. Endeavor was also associated with positive incremental QALY gains, and therefore had an incremental cost-effectiveness ratio of around £11,200/QALY.

Table 0.3 Base-case model results

	Endeavor	**Driver**	**Incremental**
Costs	£6,127	£5.830	£297
QALYs	3.8242	3.7936	0.0306
Incremental cost-effectiveness ratio (£/QALY):			**£9,689**

Results of the probabilistic analyses were in line with the deterministic findings. As shown in Figure 1.1, differences between the two stents were small. However, using a £20,000/QALY or a

£30,000/QALY threshold, Endeavor had a 76% and 86% probability of being cost-effective compared to Driver, respectively (see Figure 1.2).

Figure 0.1 Probabilistic analysis results on the cost-effectiveness plane

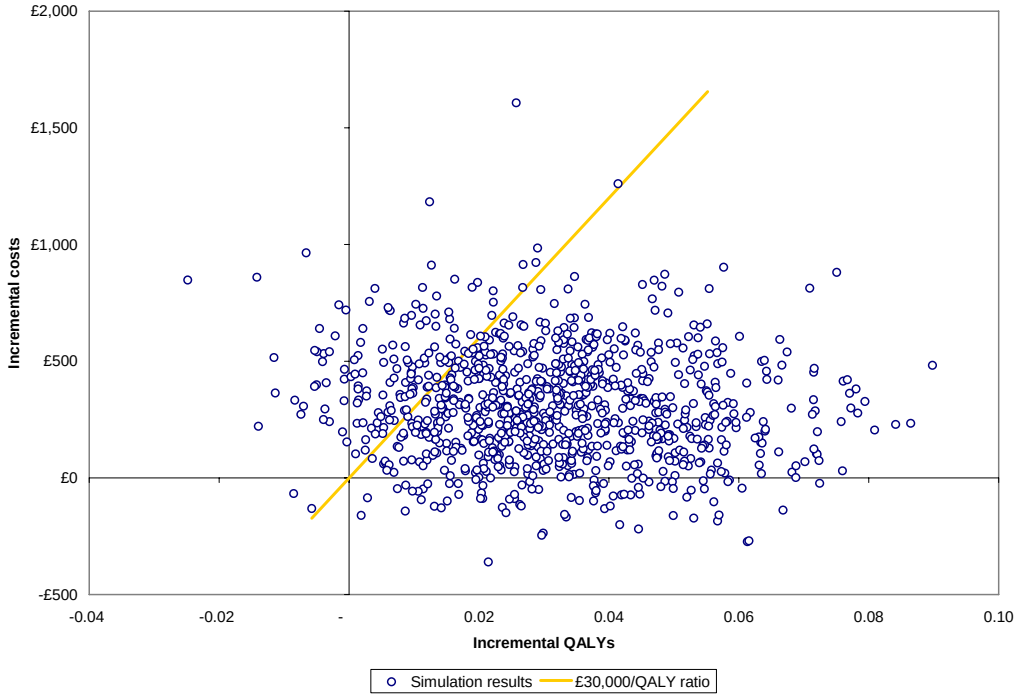
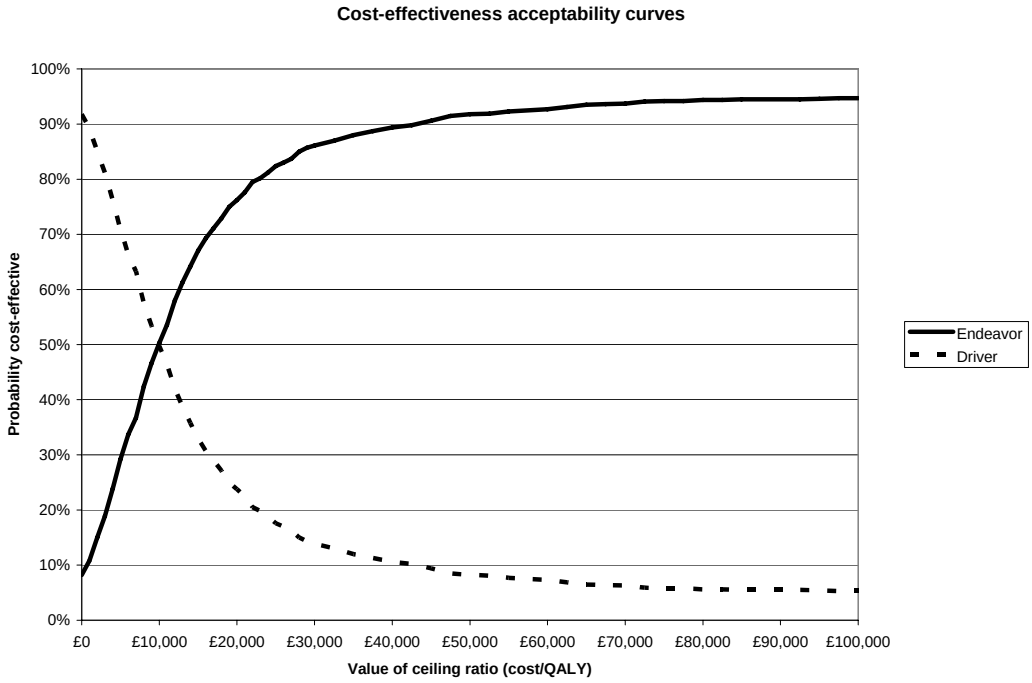


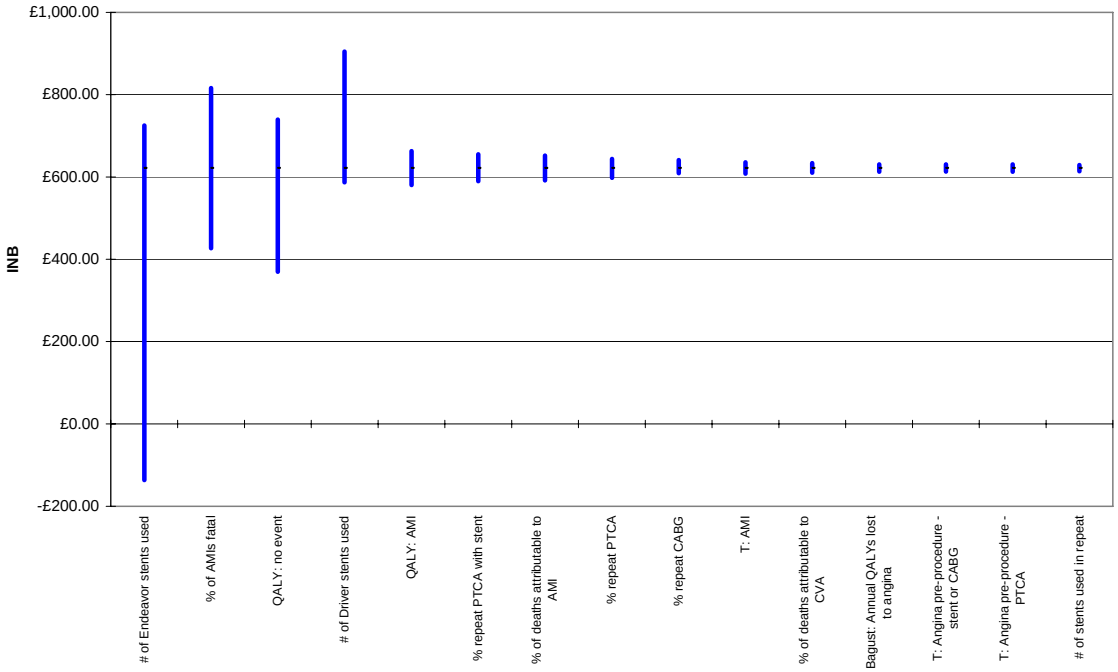
Figure 0.2 Cost-effectiveness acceptability curve of Endeavor compared to Driver



The base-case analysis assumed that there is no difference between the two stents after the first year. If Endeavor is assumed to follow the performance of other DES according to the odds ratios reported in a meta-analysis [Babapulle et al., 2004] in years 3 to 5, its ICER versus Driver became £8,248/QALY gained.

One way sensitivity analyses were also conducted on all model parameters using the range of ± 2 standard deviations. These analyses revealed that only the number of stents used in the index procedure could cause the ICER of Endeavor to increase above £30,000/QALY (as shown in Figure 1.3). If the number of stents used in the index procedure increased to 2 for both Driver and Endeavors, the ICER was £25,217/QALY, while only if the same patient randomised to different treatments would require 2 Endeavor stents but only 1 Driver stent would the ICER increase to £35,594/QALY.

Figure 1.3 Tornado diagram of the most influential variables on the incremental net benefit at £30,000/QALY threshold



References:

Babapulle MN, Joseph L, Bélise P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004;364:583-91.

Fajadet J, Wijns W, Laarman G-J, Kuck K-H, Ormiston J, Munzel T, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for threatment of native coronary artery lesions: Clinical and angiographic results of the ENDEAVOR II trial. Circulation 2006;114:798-806.

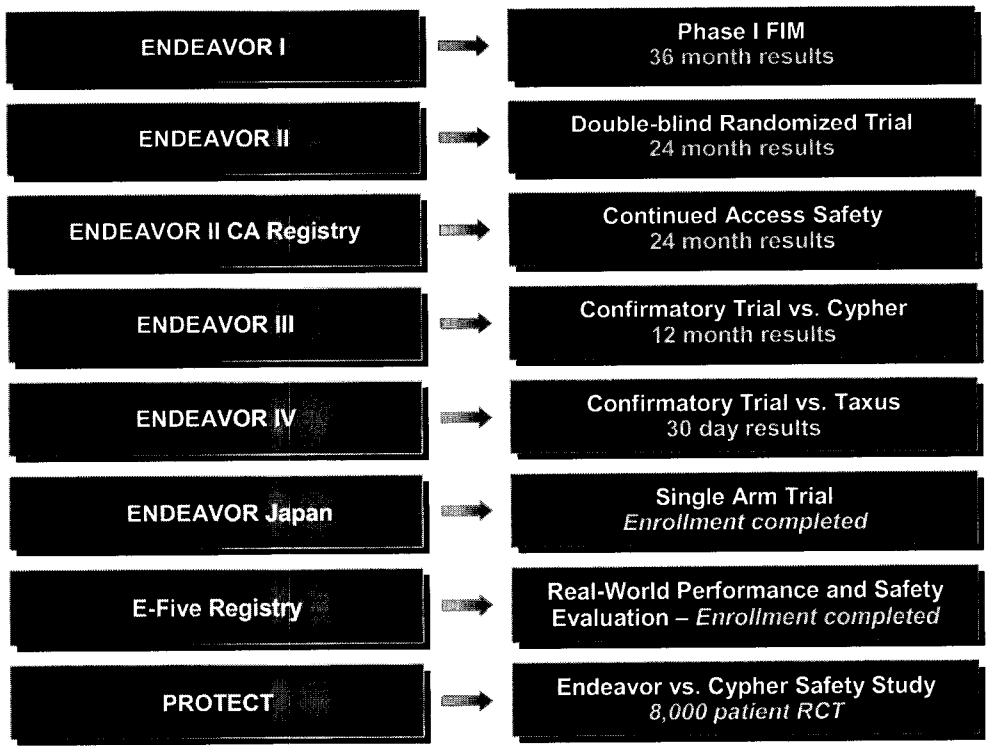
Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease – A randomized controlled trial. JACC 2006;48:2440-7.

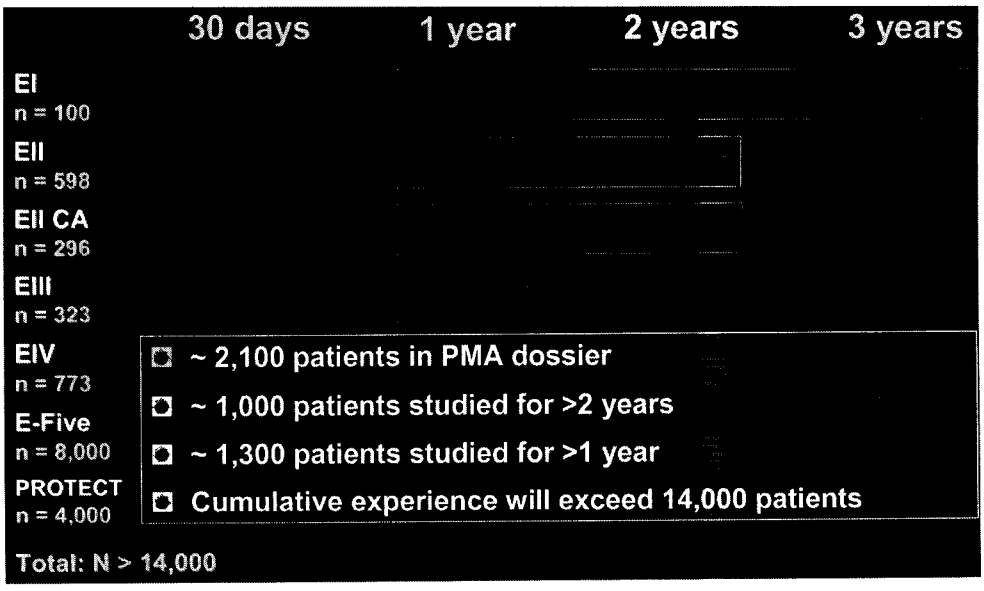
Kiemeneij FK, Serruys PW, Macaya C, Rutsch W, Heyndrickx G, Albertsson P, et al. Continued benefit of coronary stenting versus balloon angioplasty: Five-year clinical follow-up of Benestent-I trial. *Interventional Cardiology* 2001;37:1598-603.

Appendix 2

In this section, we will present all the clinical evidence that has been gathered on the Endeavor drug eluting stent since our original submission in July 2005.

Endeavor is part of an extensive and robust clinical program, including ~14,000 patients in RCTs and registries (real world)





The Endeavor clinical profile (EI, EII & EIII) is encouraging with **sustained safety and efficacy** in more than 1300 patients followed for >2years

- Deliverability documented in multiple patient populations and trials
- **Efficacy maintained out to 24 months**
- **Safety that may be unique among the DES programs**

DELIVERABILITY

Study	ENDEAVOR Combined
Procedure Success	97.5% (N = 1,304)
Lesion Success	99.8% (N = 1,305)
Device Success	98.8% (N = 1,309)

Lesion success Attainment of <50% in-stent residual percent diameter stenosis of the target lesion using any percutaneous method

Device success Attainment of <50% in-stent residual percent diameter stenosis of the target lesion using only the assigned device

Procedure success Attainment of <50% in-stent residual percent diameter stenosis of the target lesion and no in-hospital MACE

EFFICACY

We will first of all present the combined efficacy in all the patients (> 1300 patients) followed for >1year. We will then report the results of EII at 2 years, EI at 3 years, and EIII at 1 year.

Endeavor combined clinical program

Endeavor combined clinical program - Baseline characteristics

	EI n=100	EII n=598	EII CA n=296	EIII n=323	Combined N=1317
Diabetics (%)	16.0	18.2	25.8	29.7	22.5
RVD (mm)	2.96	2.74	2.63	2.75	2.73
Lesion length (mm)	10.94	14.05	16.49	14.98	14.59
B2/C lesions (%)	49	78.4	74.4	67.4	72.5

Endeavor combined clinical program - Angiographic and IVUS results

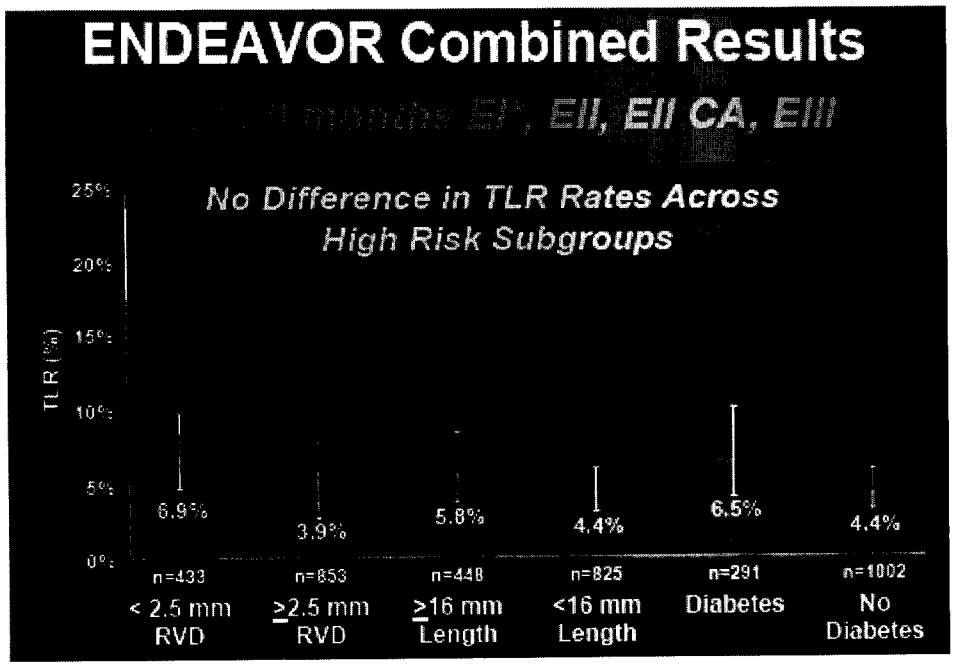
Endpoints	EI	EII	EII CA	EIII	Combined
In-stent LL (mm)	0.58	0.62	0.58	0.62	0.61
In-segment LL (mm)	0.43	0.36	0.39	0.36	0.37
In-stent ABR (%)	4.3	9.5	15.4	9.7	9.9
% Diameter stenosis	21.75	27.91	27.67	24.90	26.01
% vol obstruction	9.73	17.34	16.78	15.94	14.96
Late Incomplete Apposition	0	0	0	0.5	0.3

Endeavor combined clinical program - TLR rates at 9 and 12 months

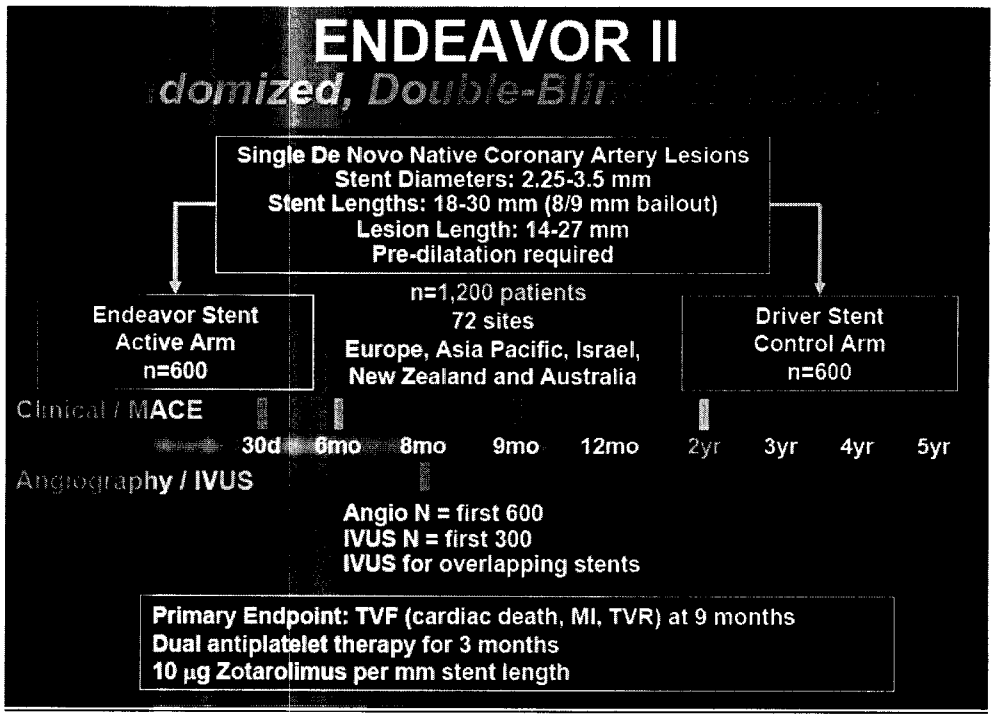
	EI n = 98	EII n = 590	EIICA n= 292	EIII n = 320	Combined n=1300
TLR at 9 months	2%	4.6%	5.1%	6.2%	**4.9%**
TLR at 12 months	2%	5.9%	6.5%	6.6%	**5.9%**

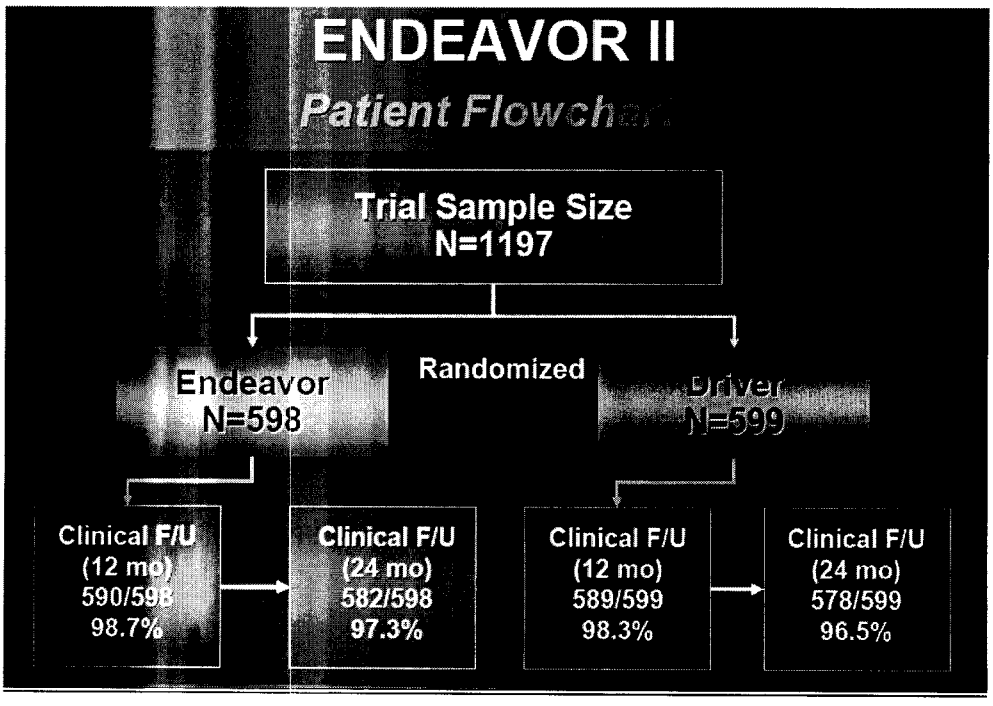
Endeavor combined clinical program – clinical events at 12 months

	EI n = 98	EII n = 590	EIICA n= 292	EIII n = 320	Combined n=1300
TLR	2%	5.9%	6.5%	6.6%	**5.9%**
TVR (non-TLR)	0	2.0%	5.8%	6.6%	**3.8%**
TVF	2%	10.0%	15.8%	12.8%	**11.4%**
MACE	2%	8.8%	12.4%	7.8%	**8.8%**
Death	0	1.4%	0.7%	0.6%	**0.9%**
MI	1%	2.7%	5.5%	0.6%	**2.7%**
Q MI	0	0.3%	0.3%	0	**0.2%**
Non Q MI	1%	2.4%	5.1%	0.6%	**2.5%**



EII pivotal study





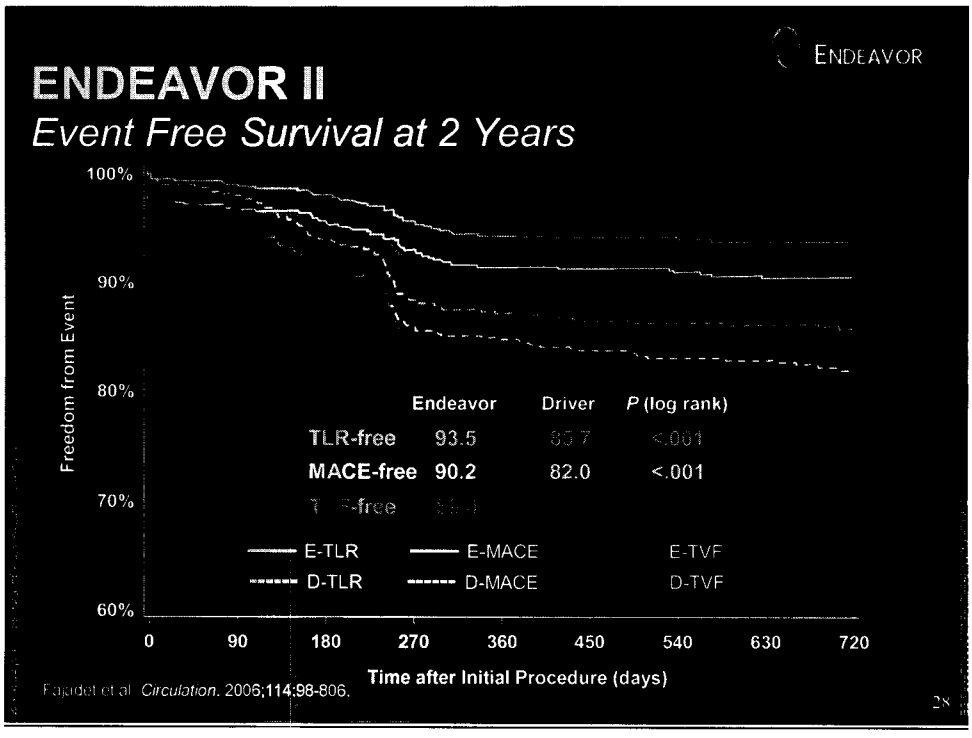
For the primary endpoint, the Endeavor drug eluting stent showed its superiority over the bare metal stent Driver, with a reduction of the TVF by 47.7% at 9 months and by 44.3% at 2 years.

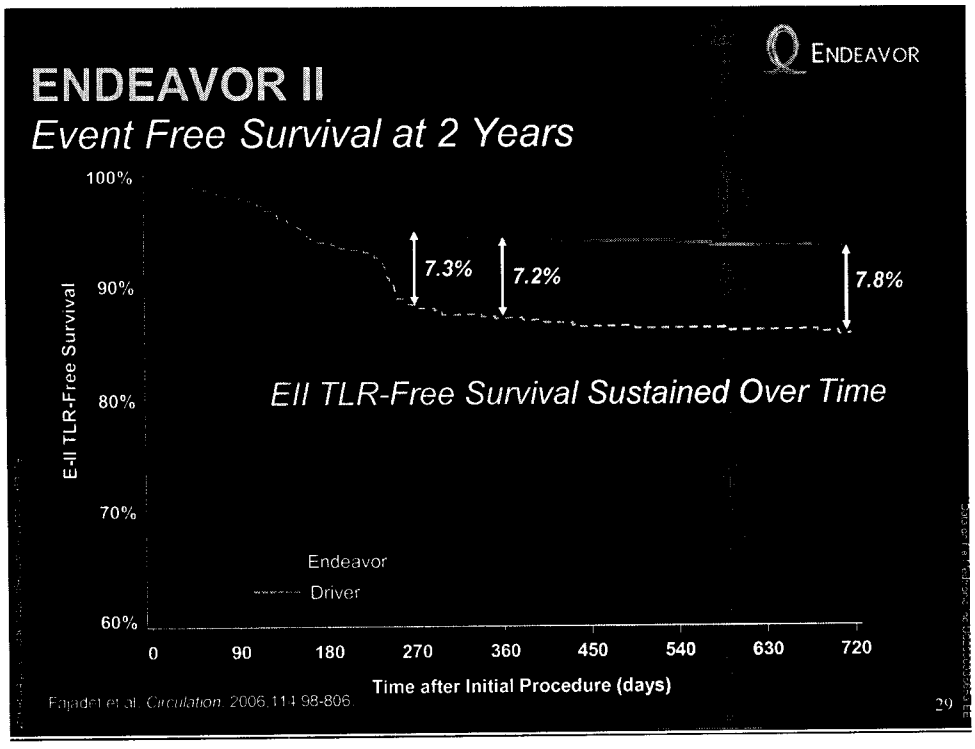
EII – Primary endpoint at 9 and 24 months

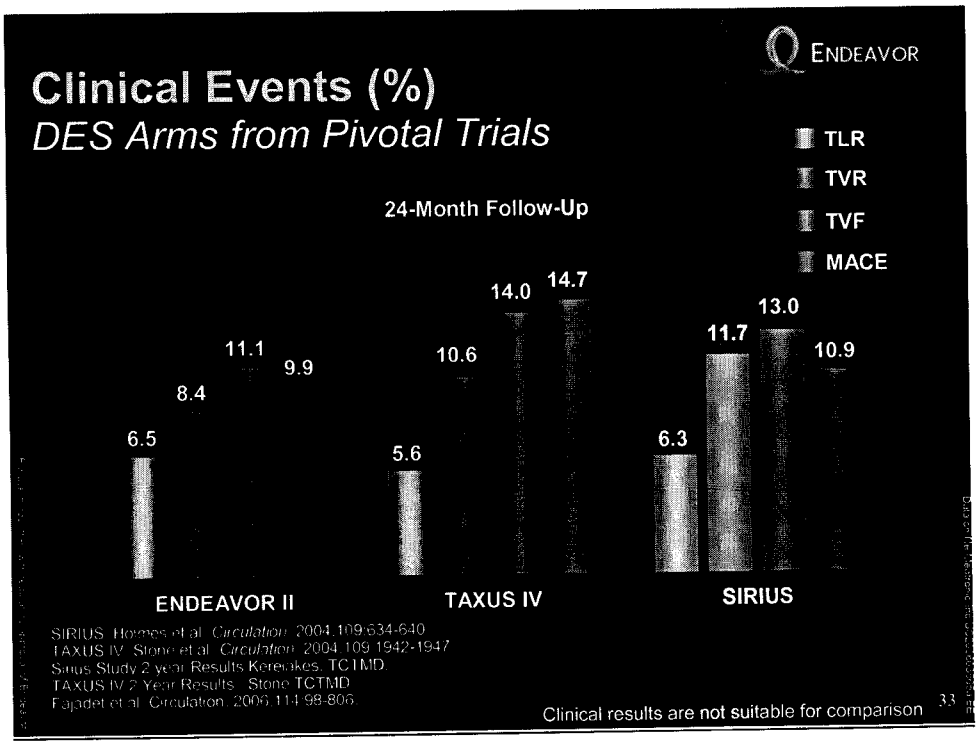
Endpoint	DRIVER™	ENDEAVOR™	p
TVF 9 months	15,1%	7,9%	< 0,0001
TVF 24 months	20,1%	11,2%	<0,001

EII – clinical events at 9 and 24 months

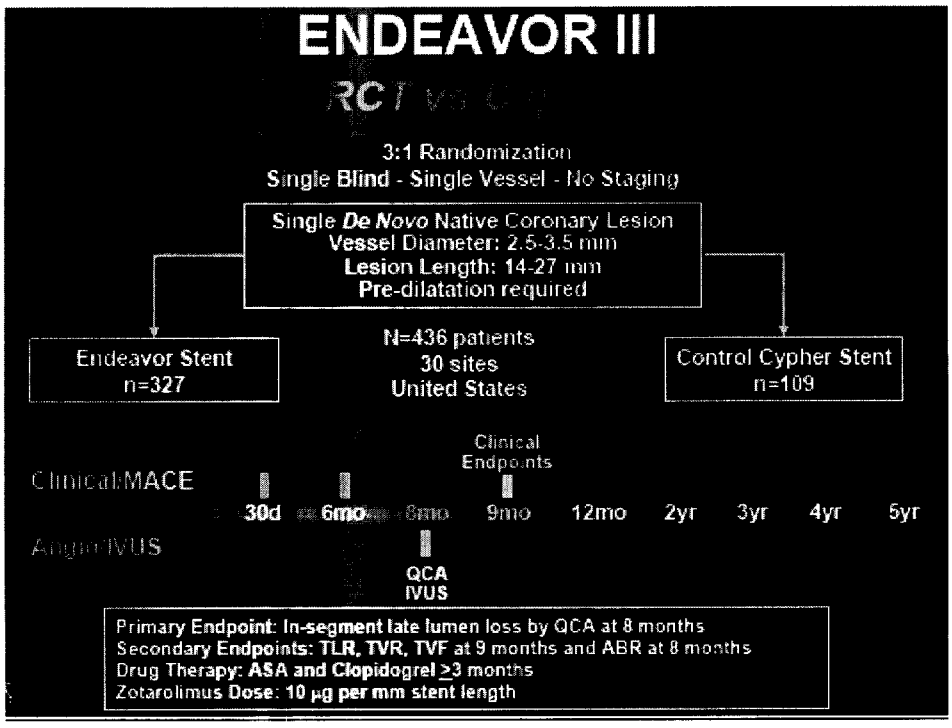
	DRIVER™ (n=585)		ENDEAVOR™ (n=582)		P
	9 months (n=591)	24 months (n=578)	9 months (n=592)	24 months (n=582)	
TLR	11,8%	**14,7%**	4,6%	**6,5%**	<0,001
TVR	12,5%	**16,6%**	5,6%	**8,4%**	<0,001
Death	0,5%	**2,2%**	1,2%	**2,1%**	NS
MI	3,9%	**4,0%**	2,7%	**2,9%**	
Q MI	0,9%	**0,9%**	0,3%	**0,3%**	NS
Non Q MI	3,1%	**3,1%**	2,4%	**2,6%**	NS
CABG	0,0%	**0,0%**	0,0%	**0,0%**	--
Total MACE	14,4%	**18,7%**	7,3%	**10,0%**	<0,001

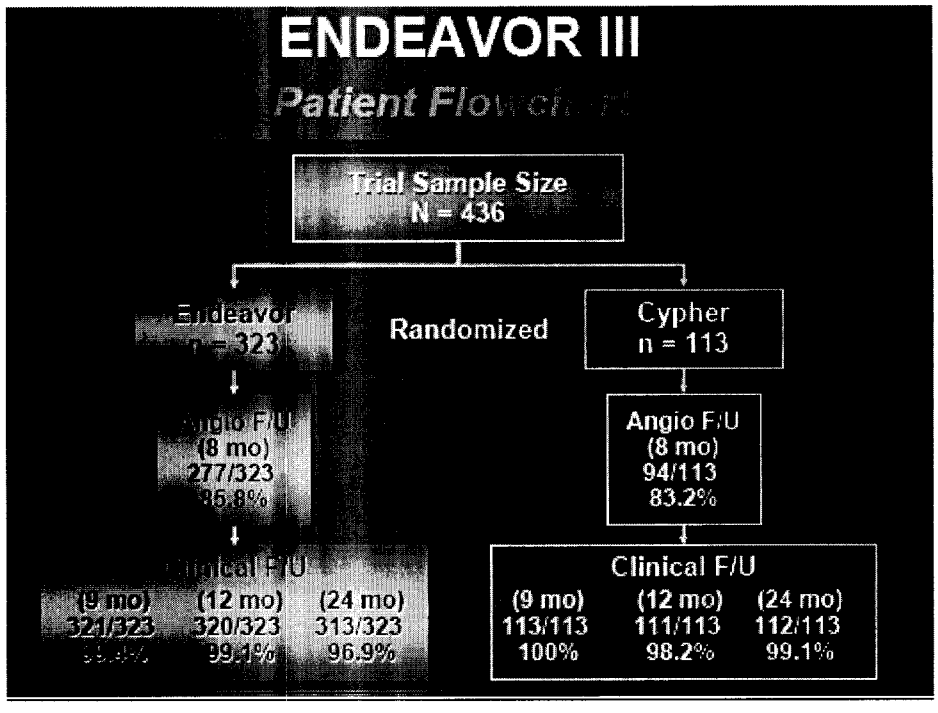



ENDEAVOR
ENDEAVOR II
Event Free Survival at 2 Years
100%
90%
80%
70%
60%
E-II TLR-Free Survival
7.3%
7.2%
7.8%
EII TLR-Free Survival Sustained Over Time
Endeavor
Driver
0
90
180
270
360
450
540
630
720
Time after Initial Procedure (days)
Fajadet et al. Circulation. 2006;114:98-806.
29


ENDEAVOR
Clinical Events (%)
DES Arms from Pivotal Trials
TLR
TVR
TVF
MACE
24-Month Follow-Up
6.5
8.4
11.1
9.9
5.6
10.6
14.0
14.7
6.3
11.7
13.0
10.9
ENDEAVOR II
TAXUS IV
SIRIUS
SIRIUS Holmes et al. Circulation. 2004;109:634-640
TAXUS IV Stone et al. Circulation. 2004;109:1942-1947
Sirius Study 2 year Results Kereiakes, TCTMD
TAXUS IV 2 Year Results Stone TCTMD
Fajadet et al. Circulation. 2006;114:98-806
Clinical results are not suitable for comparison
33

EIII





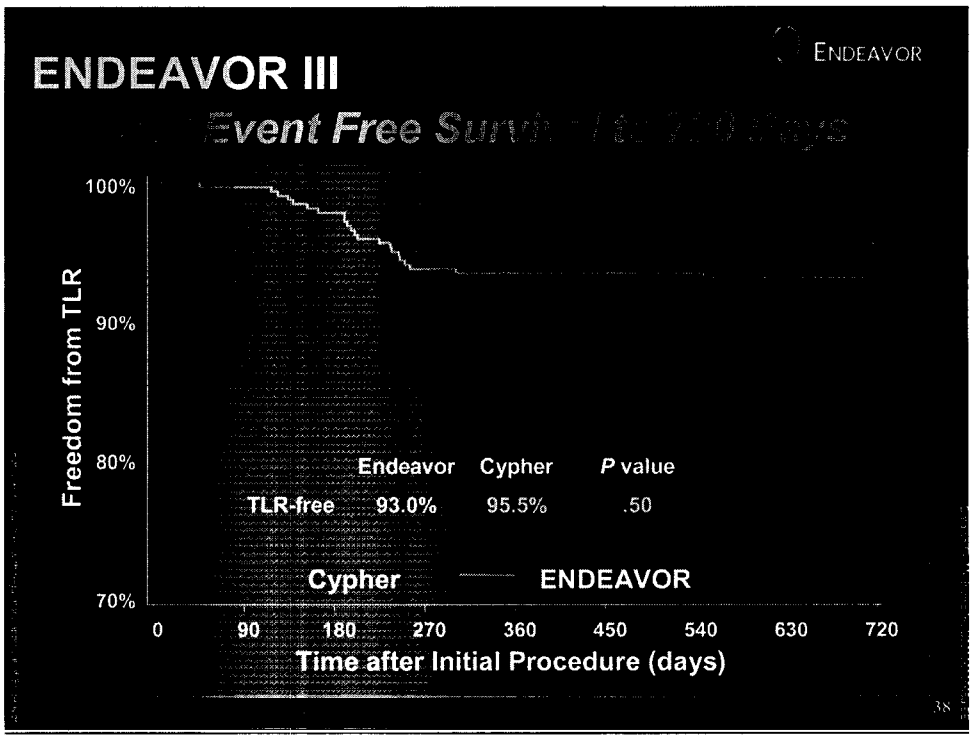
EIII – Revascularisation rates of Endeavor and Cypher at 24 months

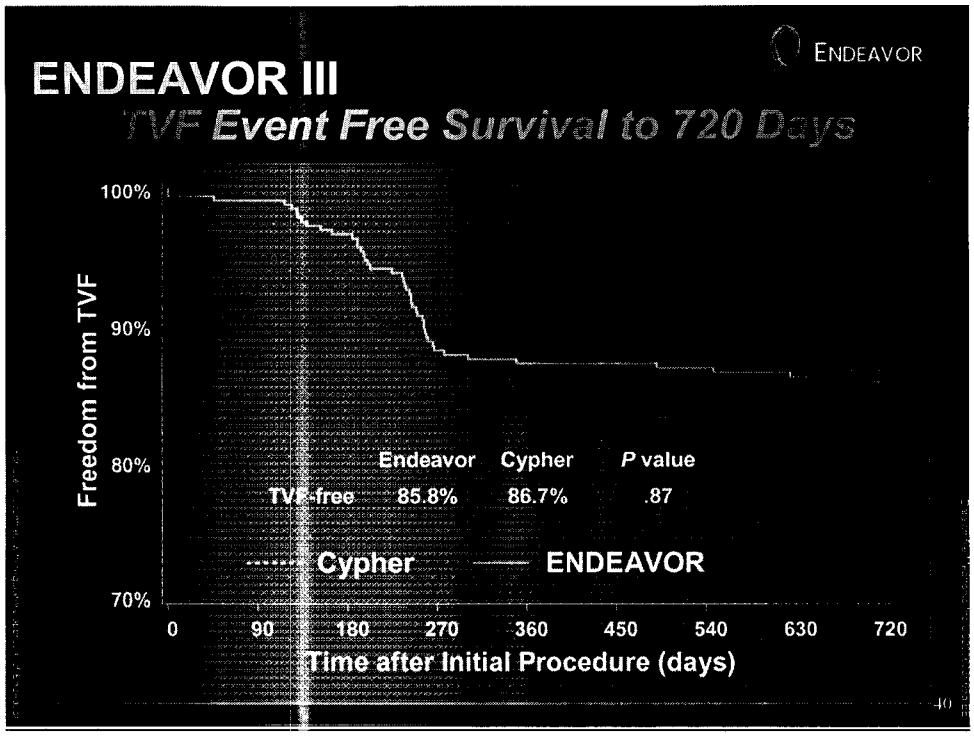
24 months	ENDEAVOR™ (n= 313)	CYPHER™ (n=112)	p

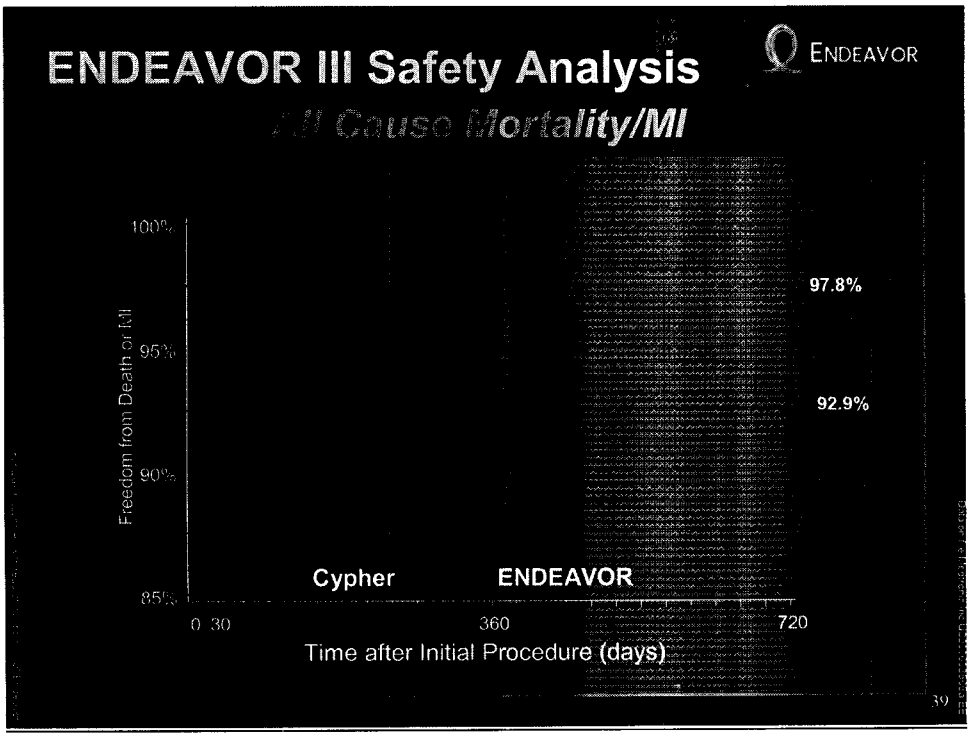
TVF	**14.4%**	13.4%	0.88
TLR	**7.0%**	4.5%	0.5
TVR (non–TLR)	**8.3%**	6.3%	0.54

EIII – Clinical events for Endeavor and Cypher at 12 and 24 months

		ENDEAVOR™ (n=323)	CYPHER™ (n=113)	p
TLR	24 months	**7.0%**	4.5%	0.5
TVR	24 months	**8.3%**	6.3%	0.54
Death (all causes)	12 months	**0.6%**	0	1.00
	24 months	**1.6%**	4.5%	0.14
MI %	12 months	**0.6%**	3.5%	0.04
	24 months	**0.6%**	3.6%	0.04
Q- MI %	12 months	**0**	0	--
	24 months	**0**	0	--
Non –Q MI %	12 months	**0.6%**	3.5%	0.04
	24 months	**0.6%**	3.6%	0.04


ENDEAVOR III
ENDEAVOR
Event Free Survival to 720 Days
100%
90%
80%
70%
Freedom from TLR
Endeavor Cypher P value
TLR-free 93.0% 95.5% .50
Cypher
ENDEAVOR
0 90 180 270 360 450 540 630 720
Time after Initial Procedure (days)
38


ENDEAVOR III
ENDEAVOR
TVF Event Free Survival to 720 Days
100%
90%
80%
70%
Freedom from TVF
Endeavor Cypher P value
TVF-free 85.8% 86.7% .87
Cypher
ENDEAVOR
0 90 180 270 360 450 540 630 720
Time after Initial Procedure (days)
40



Summary of EIII data

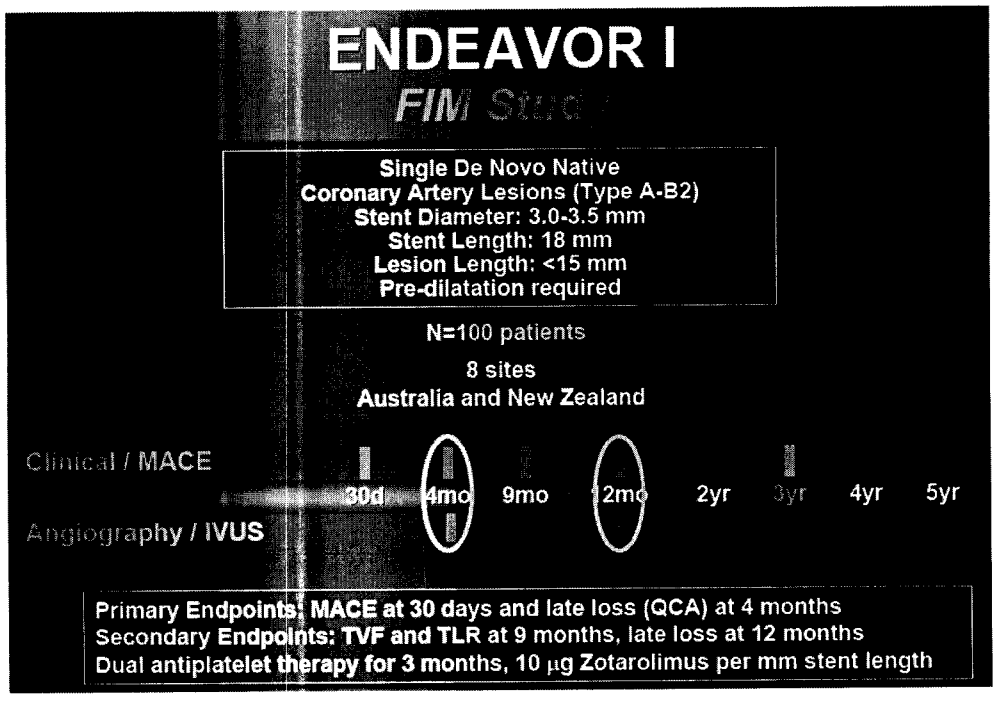
9 Months

- **Non-inferiority endpoint of in-segment late loss was missed**
- **Improved device success (deliverability) and lower in-hospital and 30-day MACE (NQWMI) resulted in a significant difference in procedure success favoring Endeavor**

24 Months

- **Safety and efficacy of the Endeavor drug-eluting stent was maintained to 24 months**
- **No significant differences in 24 month clinical outcomes (TLR, MACE, TVR and TVF)**

EI study



EI study – clinical events

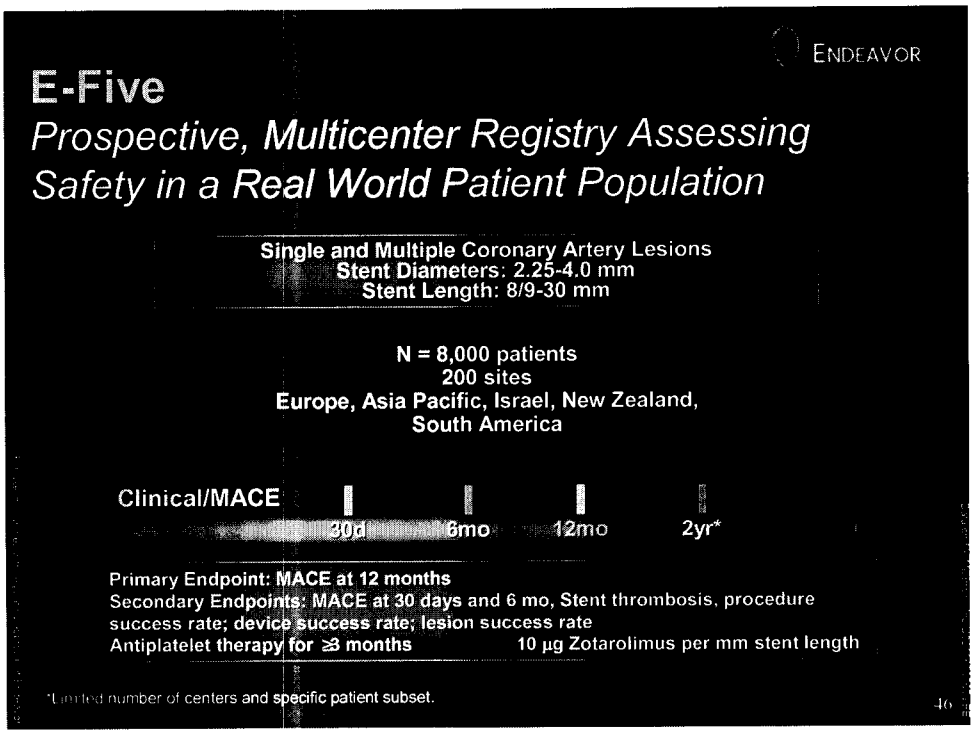
	0 – 12 months n = 98	12 – 24 months n = 98	24 – 36 months n = 97	0- 36 months n = 97
TLR	2%	0	1%	**3%**
TVR (non-TL)	0	2.0%	0	**2%**
TVF	2%	2%	0	**2%**
MACE	2%	1%	3%	**6%**
Death	0	1%*	2%*	**3%***
MI	1%	0	0	**1%**
Q MI	0	0	0	**0**
Non Q MI	1%	0	0	**1%**

*** 1x Metastatic melanoma 1x Metastatic adenocarcinoma, 1x Small cell bladder carcinoma.**

Summary of EI data

- **97% clinical follow-up to 3 years**
- **Sustained safety and efficacy**
  - **6% MACE at 36 months**
  - **3% TLR at 36 months**

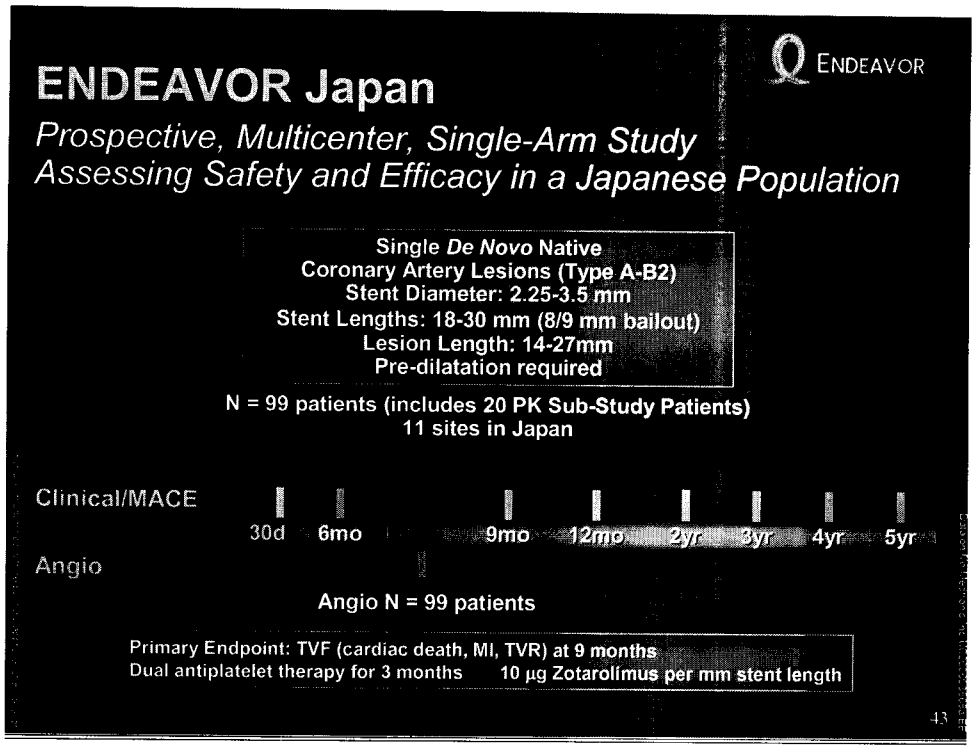
E-five



E-five – 30-days clinical events

	Non hierarchical n = 1982
TLR	0.4%
TLR-CABG	0
TLR-PTCA	0.4%
Emergent CABG	0
TVF	2%
MACE	1.7%
Death	0.9%
MI	0.9%
Q MI	0.3%
Non Q MI	0.6%

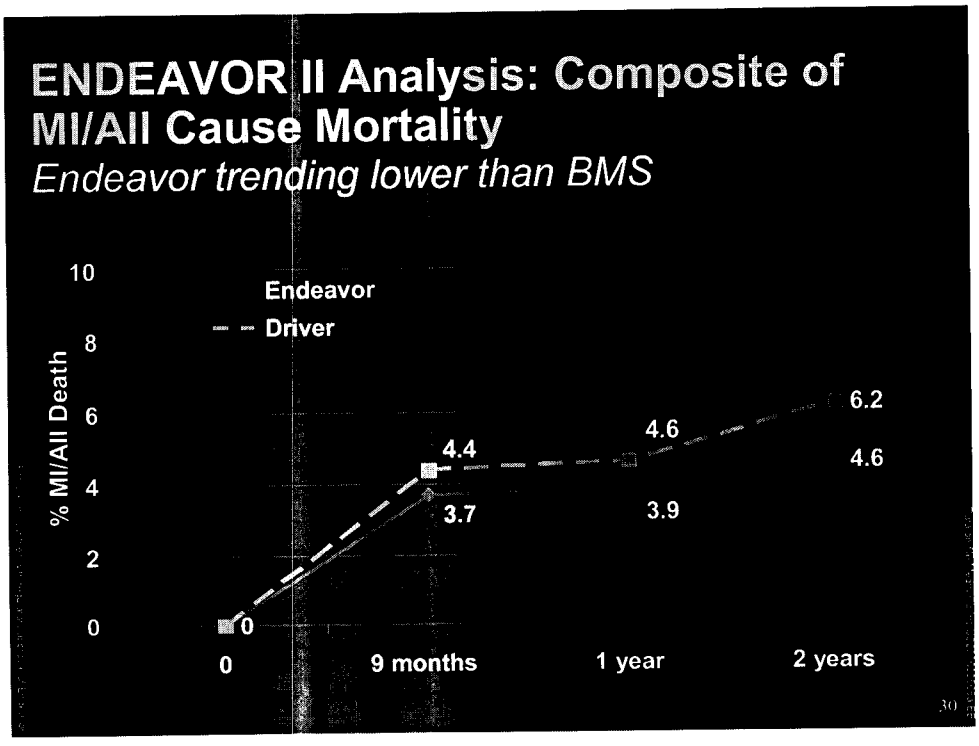
Endeavor Japan

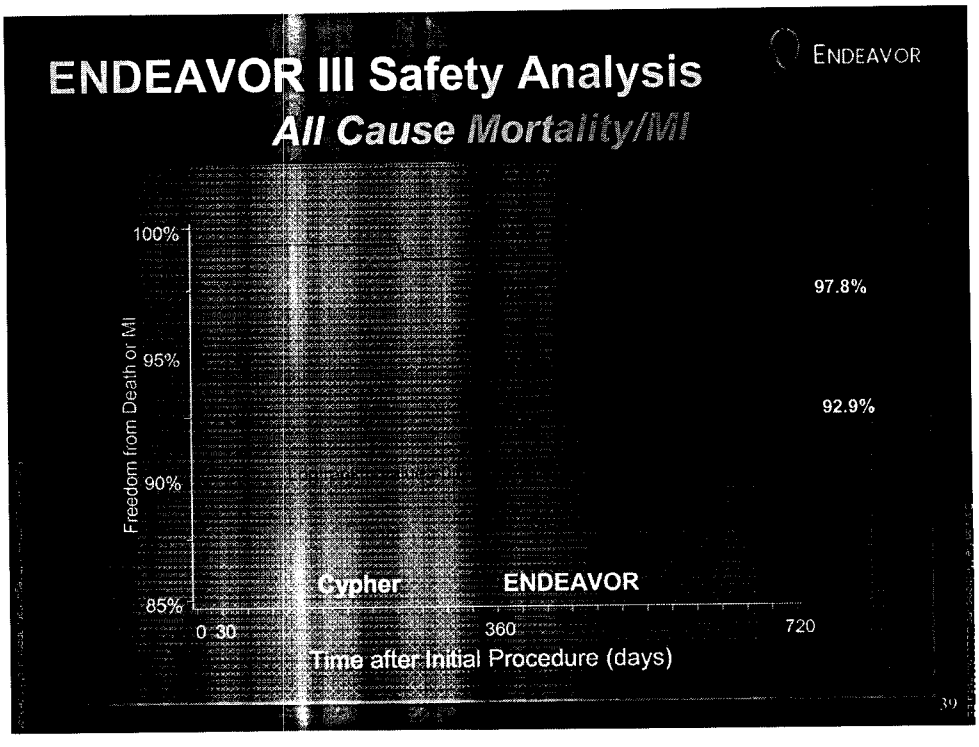


Endeavor Japan – 30-day clinical results compared to EII

	Endeavor Japan n = 99	Endeavor II n = 596	P
TLR	0	0.8%	1.000
TLR-CABG	0	0	---
TLR-PTCA	0	0.8%	1.000
Emergent CABG	0	0	---
TVR	0	1.2%	0.601
MACE	2.0%	2.9%	1.000
Death	0	0.2%	1.000
MI	2.0%	2.6%	
Q MI	0	0.3%	1.000
Non Q MI	2.0%	2.3%	1.000

SAFETY

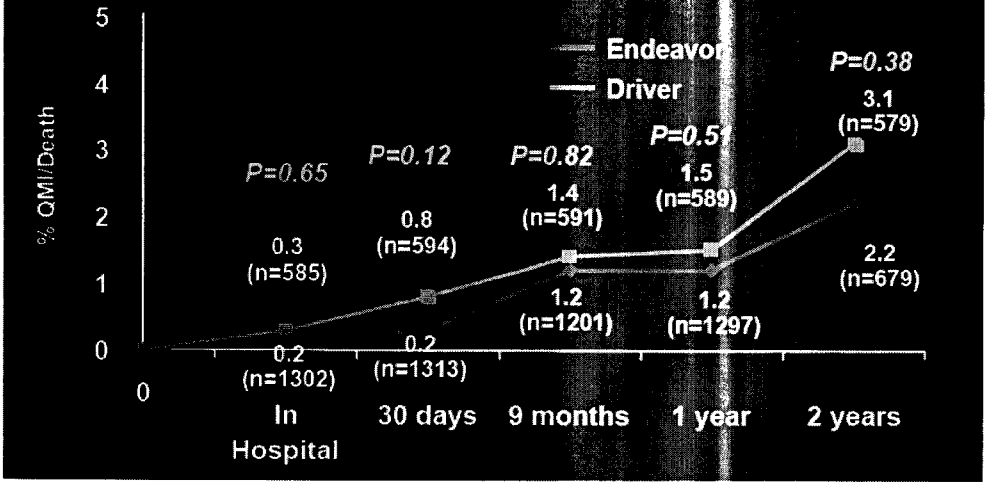

ENDEAVOR II Analysis: Composite of MI/All Cause Mortality
Endeavor trending lower than BMS
% MI/All Death
10
8
6
4
2
0
Endeavor
Driver
4.4
3.7
4.6
3.9
6.2
4.6
0
0
9 months
1 year
2 years
30


ENDEAVOR III Safety Analysis
All Cause Mortality/MI
ENDEAVOR
Freedom from Death or MI
100%
95%
90%
85%
97.8%
92.9%
Cypher
ENDEAVOR
0 30
360
720
Time after Initial Procedure (days)
39

Endeavor Safety Analysis

Composite of Death and QMI

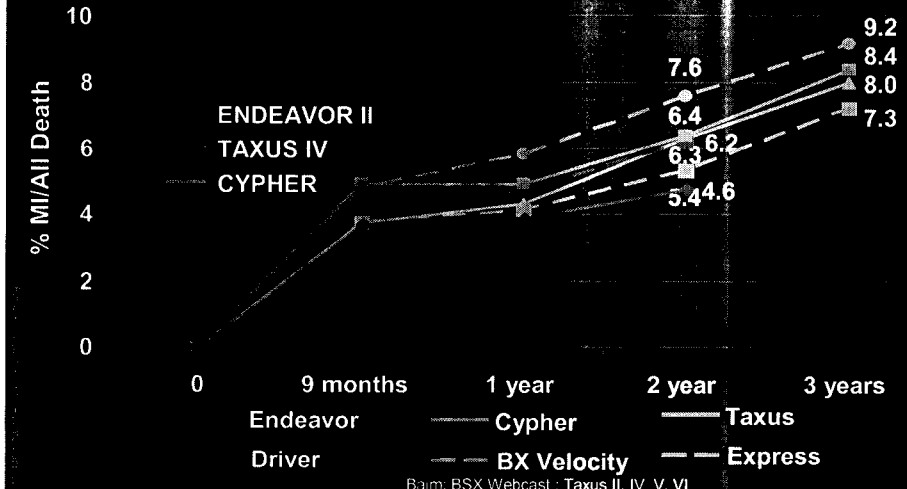
EI, EII, EII CA, and EIII vs. EII Driver



Pivotal Trials

Composite of MI/All Cause Mortality

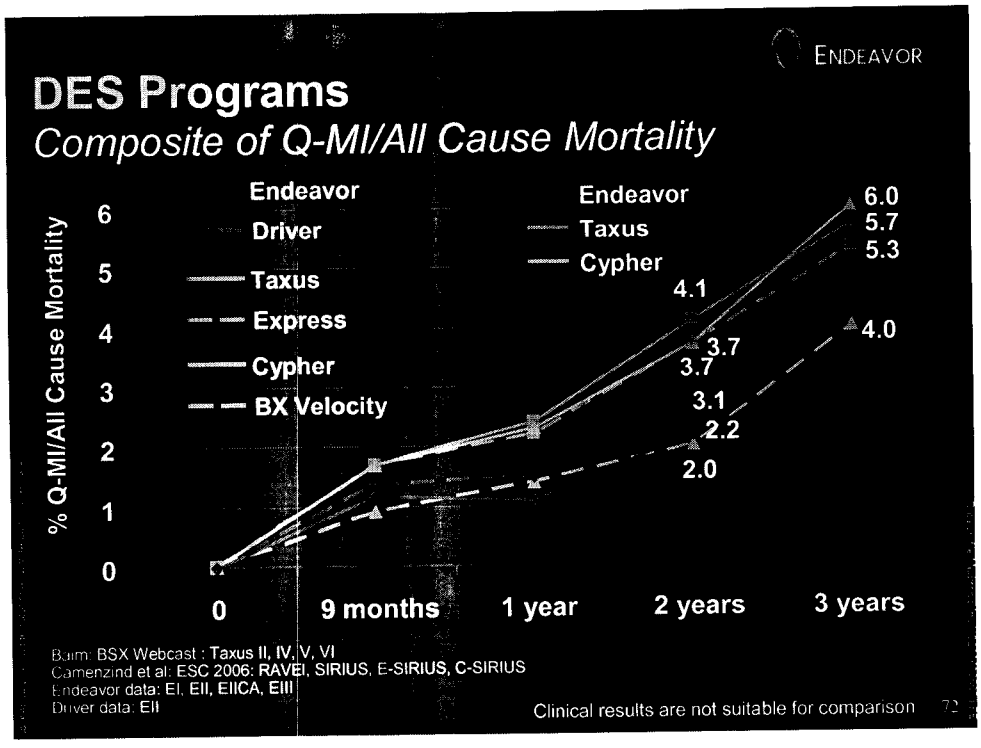
ENDEAVOR



Baim: BSX Webcast : Taxus II, IV, V, VI
Camenzind et al: ESC 2006: RAVEI, SIRIUS, E-SIRIUS, C-SIRIUS
Endeavor data: EI, EII, EIICA, EIII
Driver data: EII

TAXUS IV only reports Cardiac Death

Clinical results are not suitable for comparison



Stent thrombosis – CEC definitions

- CEC process for adjudication of ***Definite/Confirmed*** ST has been the same for all major trials of DES.
  - Acute coronary syndrome (ECG major ST abnormality or any biomarker elevation) AND
  - Angiographic or autopsy evidence of occlusion or thrombus within or adjacent to a previously stented segment. AND
  - Absence of intervening TLR
- ***Possible/Presumed ST***
  - MI in target vessel territory without angiographic evidence of thrombus or other culprit
    Variably reported among different devices and within studies of same device
  - Death from cardiac cause within 30 days

Endeavor Safety Analysis

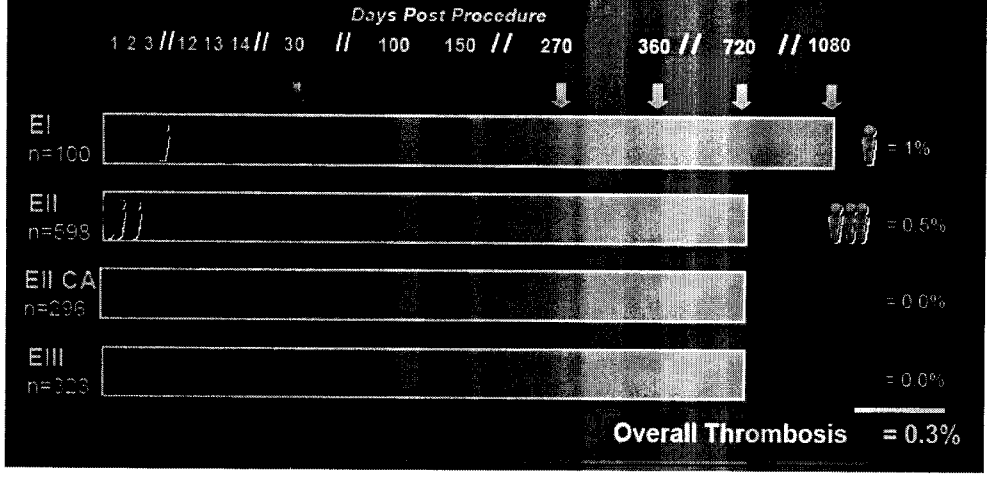
Stent Thrombosis According to Retrospective HCRI CEC Definitions

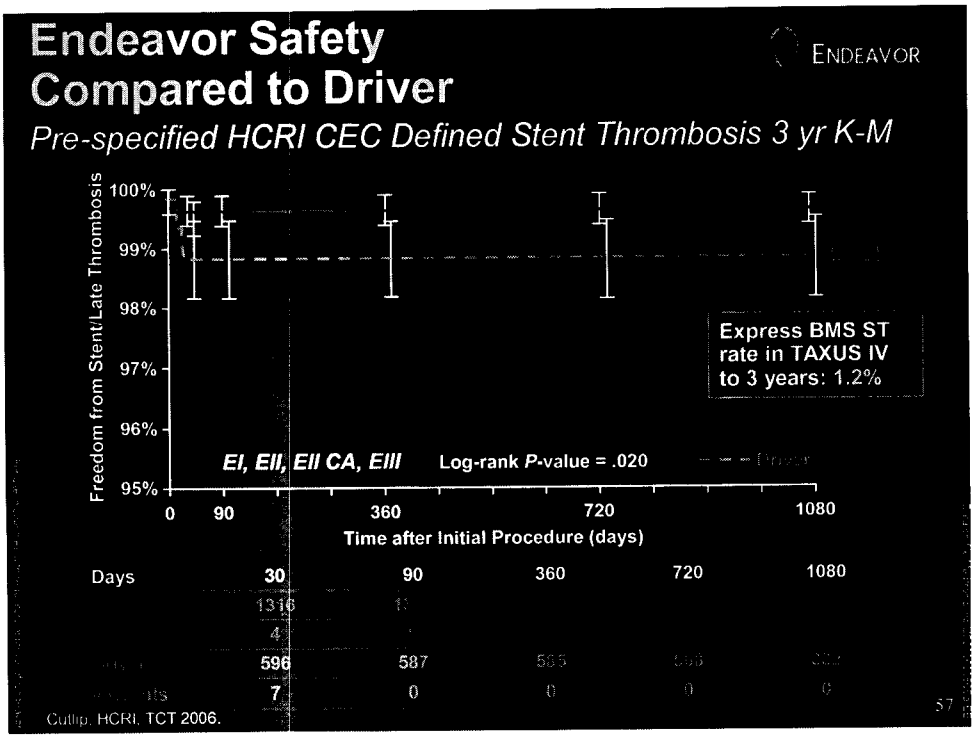
	Early (≤30days)	LaST (>30 – 365d)	V LaST (>365 d)
ENDEAVOR I n=97/100 to 3 yrs	1 (1%)	0	0
ENDEAVOR II n=583/598 to 2 yrs	3 (0.5%)	0	0
ENDEAVOR IICA n=288/296 to 2 yrs	0	0	0
ENDEAVOR III n=313/323 to 1 yr	0	0	0

Endeavor Safety Analysis

Stent Thrombosis According to Retrospective HCRI CEC Definitions

1317 patients with ≥ 2 year FU





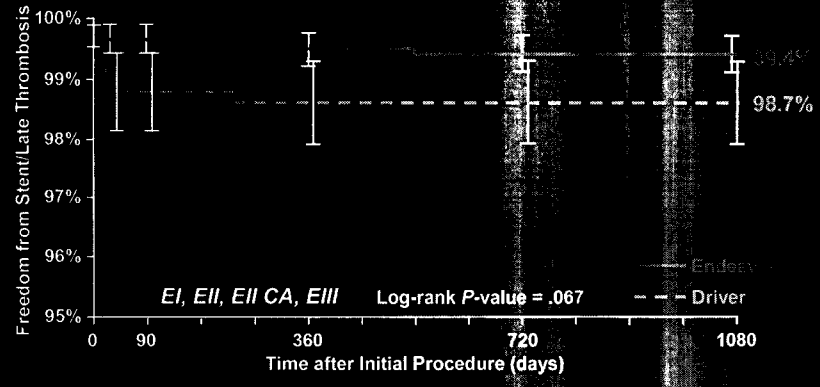
Stent thrombosis – ARC proposed definitions

- ***Definite/confirmed***
  - Acute coronary syndrome
    AND
  - Angiographic confirmation of thrombus or occlusion
    OR
  - Pathologic confirmation of acute thrombosis
- ***Probable***
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
- ***Possible***
  - Unexplained death after 30 days

Stent Thrombosis Endeavor vs Driver

ARC Definition: Definite and Probable 3 yr K-M

ENDEAVOR

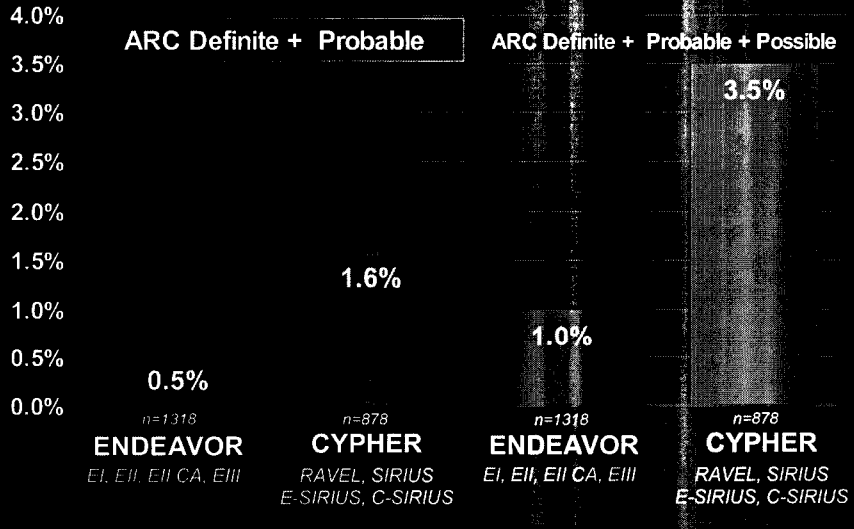


Days	30	90	360	720	1080
			593	159	0
			2	1	0
		587	585	567	382
	7	0	1	0	0

Cutlip, HCRI, TCT 2006.

Analysis: ARC Definitions of ST

Endeavor Stent Thrombosis Rate is Reported 3 Times Lower Than Cypher



Kaplan Meier % Stent Thrombosis Incidence Estimates Endeavor (3 yrs) & Cypher (4 yrs)
Metronic Data on file. Cypher data source: Don Cutlip, HCRI, TCT 2006

ARC post FDA

ENDEAVOR

	Endeavor	Driver	Cypher	BX Velocity	Taxus	Express
CEC Definitions	0.3%	1.2%	1.2%	0.6%	1.3%	0.8%
ARC Def. + Prob.	0.5%	1.4%	1.5%	0.8%	1.8%	1.1%
ARC Def. + Prob. + Poss.	1.0%	3.3%	3.6%	3.3%	3.5%	3.6%

60

Endeavor is Safe, by any Analysis

ENDEAVOR

Target Lesion Revascularization	Endeavor reduces TLR by 61% vs Driver
Pre-specified Stent Thrombosis by HCRI CEC Definition	0% LaST in Pooled Clinical Trials
Re-Adjudicated Expanded ARC ST Definition	99.5% ST Free and No Difference From Driver
Death and Q-wave MI	Endeavor: 2.2% vs. Driver: 3.1%

Fajadet et al. *Circulation*. 2006;114:98-806.
Fajadet et al. *TCT*. 2006.
Cutlip. HCRI, TCT 2006.

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Available Endeavor data have

- **Demonstrated efficacy by prevention of restenosis without an increased safety risk under ARC definitions**
- **Demonstrated a lower overall death and MI rate compared with BMS**
- **Demonstrated significantly improved healing and function compared to other DES**

Most importantly, the Endeavor clinical safety profile (EI, EII and EIII) is encouraging with infrequent stent thrombosis (early and late), infrequent death and MIs, and rare IVUS late acquired incomplete stent apposition, with>1300 patients followed for > 2 years.

Through Scientific and Clinical Analysis, Endeavor is an highly effective DES that is potentially more deliverable and safer compared to other DES