DES vs BMS for “off-label” indications: a propensity-score matched outcome study

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- Dr KG Oldroyd has received speaker and consultancy fees from Boston Scientific, Medtronic and Cordis.
- Drs Eteiba, Flapan, ACH Pell, Northcote, McConnachie, Starkey, and Jennings, report no financial conflicts.

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Clinical controversy

- Case reports and pathological concern regarding late stent thrombosis in DES
- WCC conference (Sept 2006)
- Meta-analyses (study-level)
- Observational data (SCAAR, BASKET-LATE, Rotterdam-Berne)

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“On-label” outcomes

- Pooled patient-level data from RCTs
- Increases in protocol-defined late stent thrombosis (but not overall stent thrombosis)
- No difference in hard clinical end-points in patient-level analyses
- Benefits of DES are sustained to 4 years (>10% ARR)
- FDA panel concluded benefits>risks – predominantly “on-label” patients

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“Off-label” use

- Observational studies suggest
  - “Off-label” use common
  - Higher risk of stent thrombosis and MI when “off-label” and “on-label” compared
  - Many predictors of stent thrombosis in DES are “off-label”
- On-label: Stable/unstable angina, single *de novo* lesions in a native vessel, diameter 2.5-3.75mm, lesions up to 28mm (TAXUS IV)
- Off-label: MI, high risk ACS, LVSD, CRF, bifurcations, CTO, SVG, multi-lesion … excluded
- Data are limited comparing DES and BMS for “off-label” indications

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Data sources and design

- Scottish Coronary Revascularisation Registry
- Observational design – propensity-score matching
- Since 1997, database of all PCI performed in Scottish NHS facilities (>6000 PCI/year)
- Prospective data collection including demographic details, disease severity, procedural details, lesion detail etc…
- Follow-up information derived from linkage to national datasets complete up to 30 June 2006
  - CABG or repeat PCI on target vessel (TVR)
  - Myocardial infarction (ICD coding)
  - Death

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Study population

- Index PCI with a stent between Jan 03 - Sept 05
- Included if ≥1 “Off-label” indication
  - >1 lesion
  - STEMI, NSTEMI
  - CRF
  - LVSD
  - >30mm length, vessel diameter <2.5mm or >3.75mm
  - CTO, SVG, LMCA, Restenosis, Bifurcation
- Excluded
  - DES and BMS used in same procedure
  - No FU information (<3%)

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All “Off-label” patients

	Bare-metal stent n=6,394	Drug-eluting stent n=1,105	p value
Non-ST elevation myocardial infarction, n (%)	1,834 (28.6)	223 (19.7)	<0.001
ST-elevation myocardial infarction, n (%)	875 (13.7)	67 (5.9)	<0.001
Severe left ventricular dysfunction, n (%)	128 (2.0)	17 (1.5)	0.27
Chronic renal failure, n (%)	155 (2.4)	29 (2.6)	0.77
>1 lesion treated, n (%)	2,545 (39.7)	371 (32.8)	<0.001
Stented length >30mm, n (%)	1,284 (20.0)	512 (45.3)	<0.001
Stent diameter <2.5mm, n (%)	127 (2.0)	92 (8.1)	<0.001
Stent diameter >3.75mm, n (%)	1,164 (18.2)	15 (1.3)	<0.001
Left main coronary artery stenting, n (%)	121 (1.9)	71 (6.3)	<0.001
Restenotic disease, n (%)	161 (2.5)	162 (14.3)	<0.001
Bifurcation, n (%)	1,018 (15.9)	210 (18.6)	0.02
Bypass graft, n (%)	379 (5.9)	30 (2.7)	<0.001
Chronic total occlusion, n (%)	207 (3.2)	82 (7.3)	<0.001

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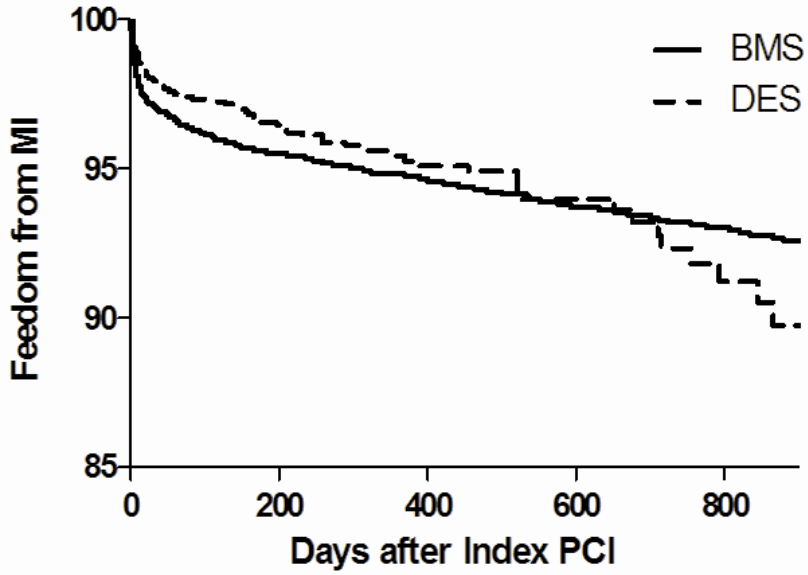
Methodological issues

Unadjusted MI – All Off-label patients



No at risk					
Bare metal stent	6398	6027	5336	4042	2715
Drug-eluting stent	1105	1072	531	274	155

1. Patient selection bias

2. Non-proportional event rate

3. Follow-up bias

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Propensity-score matching

- Conditional probability of receiving a DES on the basis of known co-variates
- PS calculated using logistic regression and 24 relevant co-variates
  - Patient factors
  - Lesion/angiographic factors
  - Time
- DES and BMS matched 1:1 on basis of PS
- Outcomes then assessed using K-M method
- Selection bias, non-proportional follow-up, and follow-up bias overcome

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Results

- 7499 “Off-label” patients
  - 72.5% of all PCI
  - 6394 BMS, 1105 DES

- After PS matching 1642 (821 pairs)
- DES group: 521 (63.4%) PES, 275 (33.5%) SES
- BMS group: 642 (78.2%) Thin-strut/cobalt chromium
- 24 months follow up (median 16 months)

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PS-matched cohorts

	Bare-metal stent n=821	Drug-eluting stent n=821	p value
Non-ST elevation myocardial infarction, n (%)	204 (24.8)	188 (22.9)	0.90
ST-elevation myocardial infarction, n (%)	60 (7.3)	64 (7.8)	0.90
Severe left ventricular dysfunction, n (%)	12 (1.5)	12 (1.5)	0.88
Chronic renal failure, n (%)	27 (3.3)	22 (2.7)	0.88
>1 lesion treated, n (%)	296 (36.0)	304 (38.4)	0.85
Stented length >30mm, n (%)	245 (31.8)	260 (33.5)	0.84
Stent diameter <2.5mm, n (%)	296 (36.0)	304 (38.4)	0.85
Stent diameter >3.75mm, n (%)	12 (1.6)	13 (1.7)	0.72
Left main coronary artery stenting, n (%)	44 (5.4)	39 (4.8)	0.57
Restenotic disease, n (%)	73 (8.9)	72 (8.8)	0.93
Bifurcation, n (%)	169 (20.6)	154 (19.4)	0.53
Bypass graft, n (%)	28 (3.4)	28 (3.4)	1.0
Chronic total occlusion, n (%)	40 (4.9)	49 (6.0)	0.33

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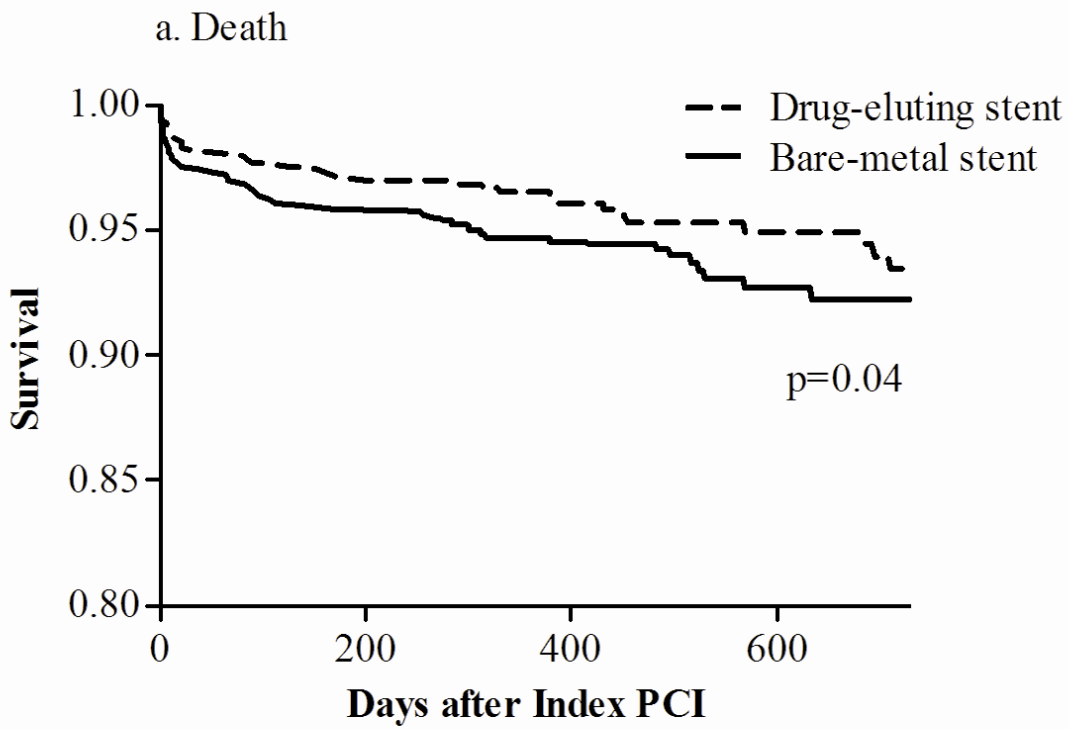
K-M survival: all-cause death



No at risk				
Bare metal stent	821	770	582	227
Drug-eluting stent	821	782	407	223

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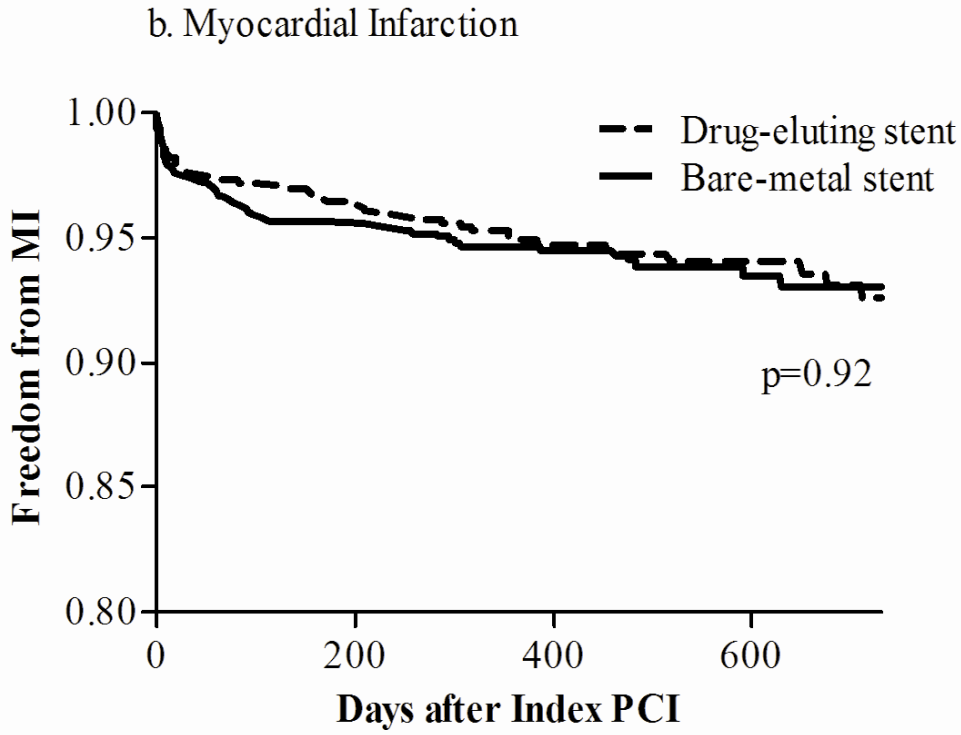
K-M survival: freedom from MI



No at risk				
Bare metal stent	821	770	582	227
Drug-eluting stent	821	782	407	223

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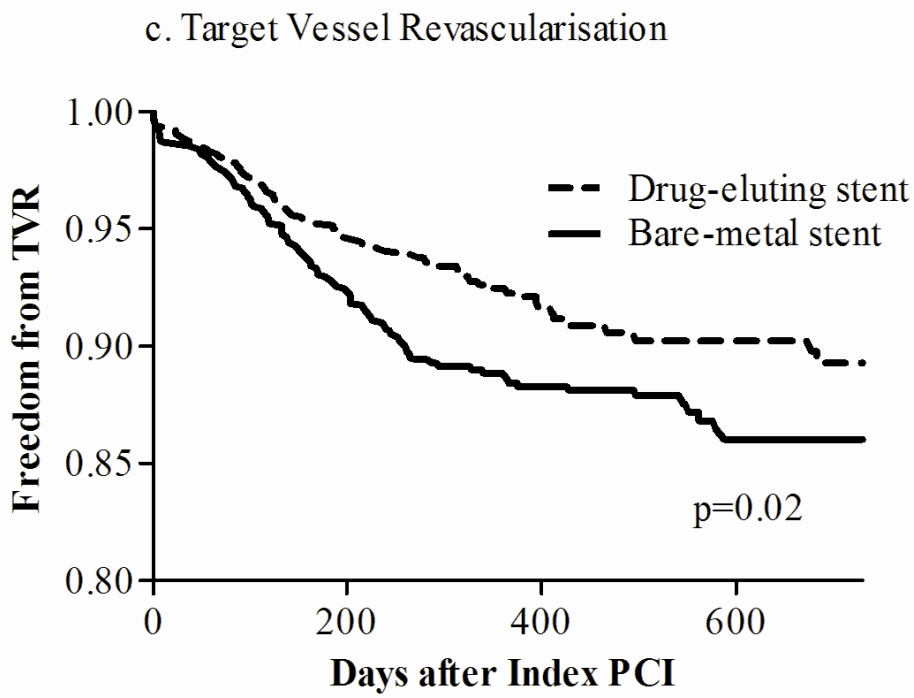
K-M survival: freedom from TVR



No at risk				
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Summary of outcomes

	Death		Myocardial Infarction		Target Vessel Revascularisation	
	BMS	**DES**	**BMS**	**DES**	**BMS**	**DES**
1 month (%)	2.4	1.8	2.8	2.4	1.3	1.1
6 months (%)	4.1	2.9	4.8	3.7	7.1	4.8
12 months (%)	5.3	3.5	5.7	5.0	11.4	7.7
24 months (%)	7.7	6.6	7.3	7.5	13.9	10.7

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Limitations

- Not a randomised controlled trial
- Registry and routine data
- Outcomes are not adjudicated
- Rely on appropriate adjustment and matching
- Unknown/unmeasured confounders – particularly all-cause death e.g. Dementia
- Some DES patients “lost” following matching
- No accurate data on stent thrombosis or clopidogrel therapy

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Strengths

- Actual clinical practice
- Group not widely studied in RCTs
- “Hard” clinical endpoints
- Comprehensive case ascertainment and outcome data largely complete and unbiased to stent type
- Thin-strut, cobalt chromium BMS, contemporary control group. Broad range of clinical indications.
- Preserves the true pattern of events and therefore retains some of the inherent advantages of experimental study design
- Overcomes non-proportional hazards that limits other types of observational analyses

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Conclusions

- Previous studies suggest “off-label” indications may have poorer clinical outcomes

- “Off-label” DES use is very common
- In Scotland, DES use is associated with reduced TVR and death and no difference in MI
- Absolute reductions in TVR rates were lower than RCTs

- Randomised controlled trials are required to inform “real world” practice and demonstrate safety of DES

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