LEADERS FREE

Biolimus-Coated vs. Bare-Metal Coronary Stents in High Bleeding Risk Patients

Hossam Mansour. MD
October 6th university

tct2015 LEADERS FREE

Background

- For ACS patients undergoing PCI current guidelines recommend in general 12 months DAPT
- High bleeding risk patients presenting with ACS undergoing PCI have never been systematically studied.
- Current guidelines recommend for these patients:

  I. Implantation of a DES with 3- 6 months DAPT

  II. Implantation of a BMS with 1 month DAPT
- The aim of this prespecified substudy was to evaluate the safety and efficacy of the BioFreedom ™ BA9 DCS followed by 1 month DAPT in high bleeding risk patients presenting with an ACS

tct2015 LEADERS FREE

LEADERS FREE ACS

Objectives

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet† (France),

$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A	187–189, 192

187: RESET: Kim BK et al, JACC 2012; 60: 1340 E-ZES 3 months DAPT
188: OPTIMIZE: Feres F et al, JAMA 2013; 310: 2510 E-ZES 3 months DAPT
189: EXCELLENT: Gwon HC et al, Circ 2012; 125: 505 DES 6 months DAPT
192: ISAR-SAFE: Schulz-Schupke S et al, EHJ 2015; 36: 1252 DES 6 months DAPT

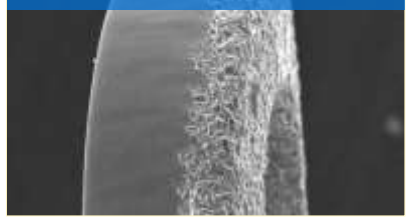
High Bleeding Risk Patients (HBR)

- Mostly excluded from device and APT trials
- Never specifically studied
- Current guideline recommendations:
  - BMS + one month DAPT
  - DES + “shortened” DAPT

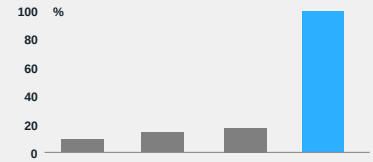
tct2015 LEADERS FREE

BioFreedom™ Drug Coated Stent (DCS)

Selectively Micro-Structured Surface Holds Drug in Abluminal Surface Structures



BA9™ Drug 10 Times More Lipophilic than Sirolimus[1]



+/- 2.8% (valid for all drugs test)

Potential Advantages:

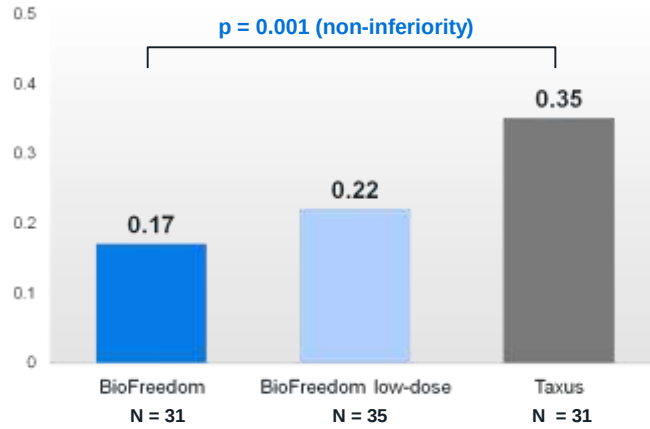
- ✓ Avoid any possible polymer-related adverse effects
- ✓ Rapid drug transfer to vessel wall (98% within one month[2])
- ✓ Safe to shorten DAPT?

1. Data on file at Biosensors Intl; 2. Tada et al., Circ Cardiovasc Interv 2010;3;174-183

tct2015 LEADERS FREE

Median In-Stent LLL at 12-month Follow-up

2nd Cohort – Primary Endpoint



Costa R et al. JACC interv (published online October 11, 2015 – DOI 10.1016/j.jcin.2015.09.008)

tct2015 LEADERS FREE

LEADERS FREE Trial Design

Prospective, double-blind randomized (1:1) trial
2466 High bleeding risk (HBR) PCI patients

BioFreedom™ DCS **vs.** **Gazelle™ BMS**

DAPT mandated for 1 month only, followed by long-term SAPT

- **Primary safety endpoint:**
  Composite of cardiac death, MI, definite / probable stent thrombosis at 1 year (non-inferiority then superiority)
- **Primary efficacy endpoint:**
  Clinically-driven TLR at 1 year (superiority)

tct2015 LEADERS FREE

Inclusion Criteria (One or More)

- Age ≥ 75 years
- OAC planned after PCI
- Baseline Hb < 11g / dl or transfusion during prior 4 weeks
- Planned major surgery (within next year)
- Cancer diagnosed or treated ≤ 3 years
- Creatinine clearance < 40 ml / min
- Hospital admission for bleeding during past year
- Thrombocytopenia (< 100.000 / mm3)
- Any prior intra-cerebral bleed
- Any stroke during the past year
- Severe liver disease
- NSAID or steroids planned after PCI
- Anticipated poor DAPT compliance for other medical reason

Determination of Trial Size

Predicted event rates in BMS control arm

- Composite safety endpoint (cardiac death, MI and ST) 8%
- Efficacy endpoint (clinically-driven TLR) 10%

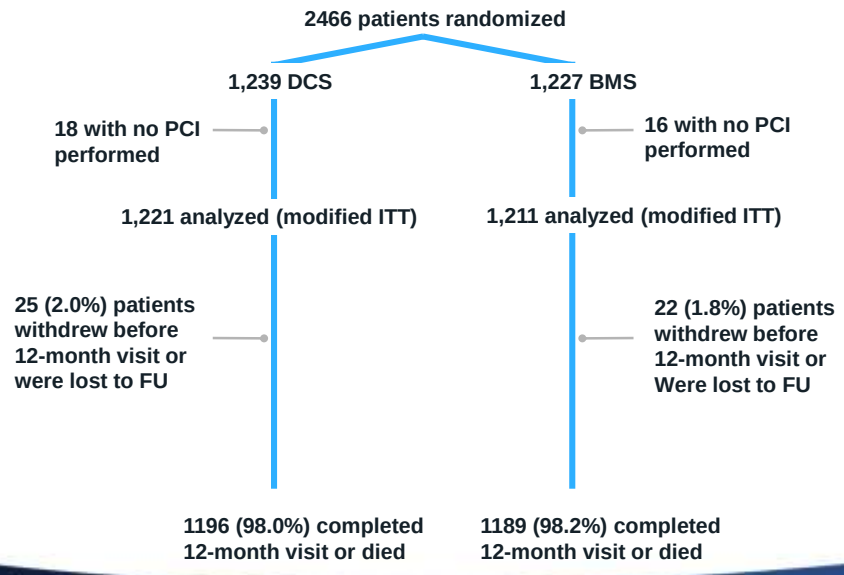
Patients per group: 1228

Endpoints

- **Safety:**
  > 80% power to demonstrate non-inferiority with margin 3.2%
- **Efficacy:**
  > 80% power to detect a 3.3% reduction in c-TLR

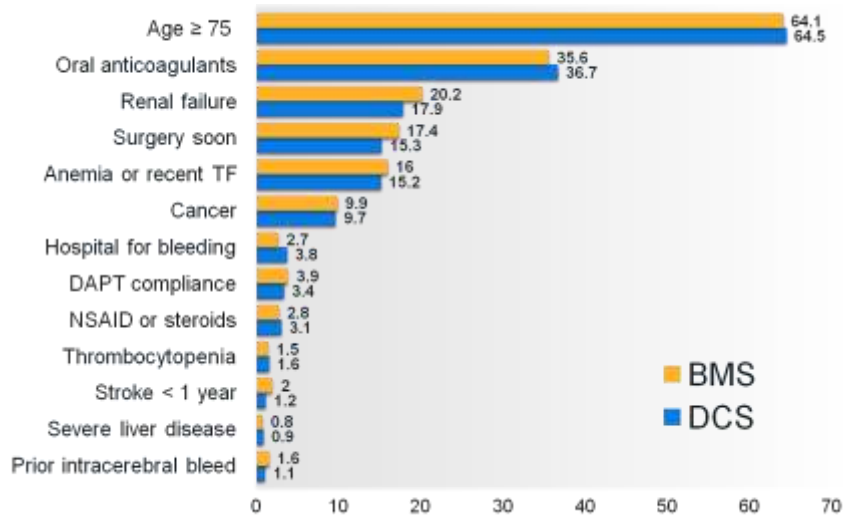
Both with one-sided alpha 0.025

Enrollment and Follow-Up



tct2015 LEADERS FREE

Inclusion Criteria Applied (1.7 criteria / patient)



tct2015 LEADERS FREE

Baseline Characteristics

	DCS (%)	BMS (%)
Mean age	75.7 + 9.4	75.7+9.3
Female gender	29.8	30.9
BMI	27.5 ± 4.8	27.2 ± 4.6
Diabetes	34.0	32.3
NSTEMI presentation	22.4	23.2
STEMI presentation	4.7	4.0
Prior MI	19.6	21.4
Prior PCI	22.2	21.9
Prior CABG	9.4	10.1
Multivessel CAD	62.9	61.6
Congestive heart failure	14.4	12.4
Atrial fibrillation	34.9	34.6
Peripheral vascular disease	15.7	15.8
Chronic obstructive lung disease	10.9	11.7

None of the baseline characteristics differ at p < 0.05

Index Procedure

	DCS (%)	BMS (%)
Radial access	60.7	58.7
Staged procedure	4.5	5.9
Multi-lesion procedure	37.8	35.3
Multi-vessel procedure	21.8	21.4
Number of treated lesions / patient	1.6 ± 0.8	1.6 ± 0.9
LMS	3.0	3.9
SVG	1.4	1.8
Bifurcation	14.9	16.0
ISR	2.4	2.6
CTO	5.0	4.4

None of the procedure characteristics differ at p < 0.05

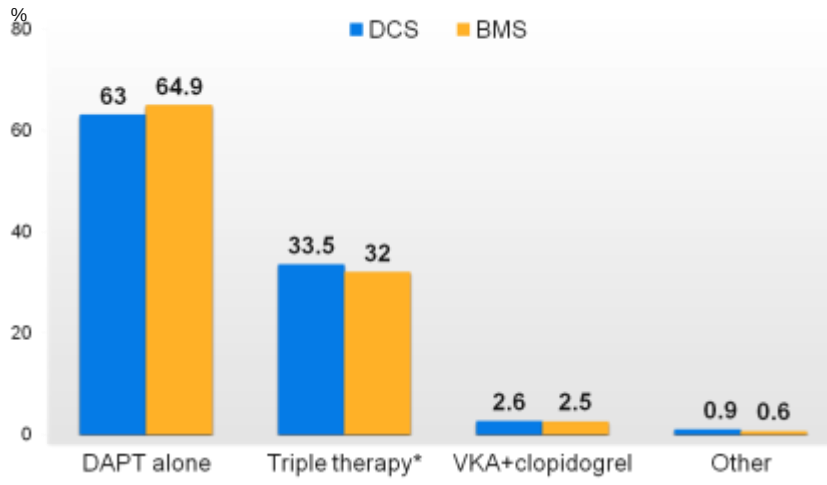
Index Procedure (Continued)

	DCS	BMS
Mean stent diameter	3.0 ± 0.4	3.0 ± 0.4
Mean total implanted stent length / patient	34.5 ± 23.1	33.4 ± 23.4
Mean number of stents implanted / patient	1.9 ± 1.1	1.8 ± 1.2
Lesion success	97.7	98.0
Device success	97.7	97.6
Procedure success	94.4	93.7
UFH during procedure	90.5	89.4
LMWH during procedure	8.4	8.8
Bivalirudin during procedure	1.1	1.8
2b3a blocker during procedure	2.0	1.2

None of the procedure characteristics differ at p < 0.05

tct2015 LEADERS FREE

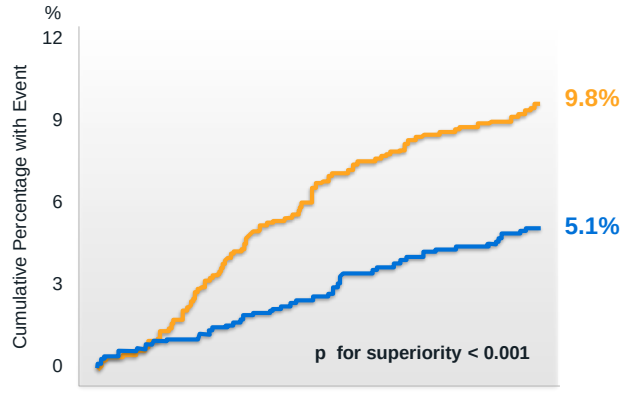
Antithrombotic Medication at Discharge



None of the regimens differ at p < 0.05
* Any oral anticoagulant + DAPT

tct2015 LEADERS FREE

Primary Efficacy Endpoint (Clinically-Driven TLR)



Number at Risk					
DCS	1221	1167	1130	1098	1053
BMS	1211	1131	1072	1034	984

390 days chosen for assessing primary EP to capture potential evens driven by the 360 day FU contact

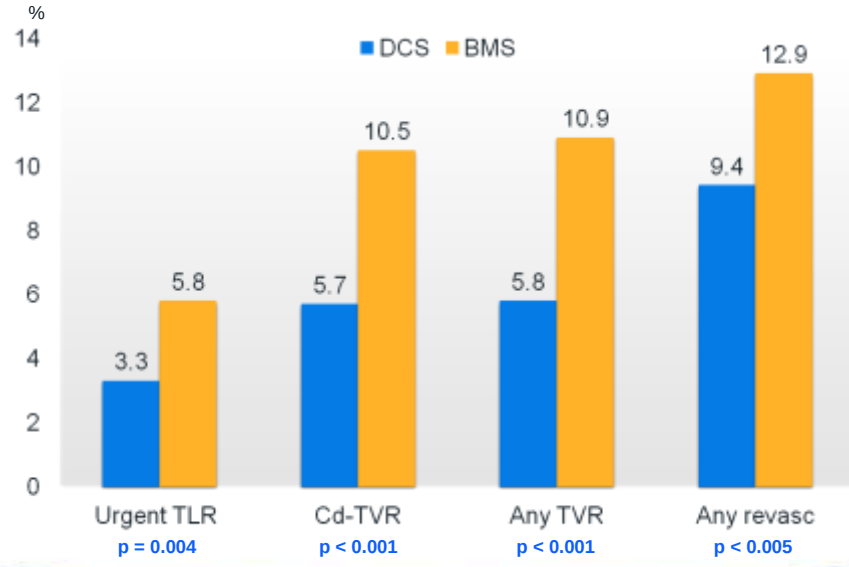
Primary Efficacy Endpoint

Primary Efficacy Endpoint	DCS (n=1221)	BMS (n=1211)
Clinically driven TLR at 390 days	**59 (5.1%)**	**113 (9.8%)**

Difference:

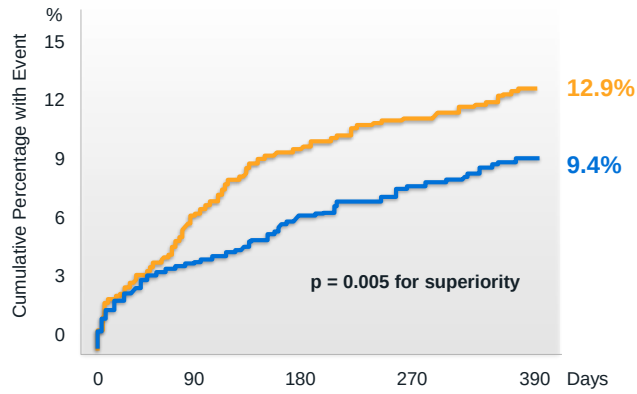
- -4.8% (95% CI = -6.9% to -2.6%)
- HR 0.50, (95% CI = 0.37 – 0.69)
- p<0.001 for superiority

Secondary Efficacy Endpoints



tct2015 LEADERS FREE

Primary Safety Endpoint (Cardiac Death, MI, ST)



Number at Risk

DCS	1221	1146	1105	1081	1045
BMS	1211	1115	1066	1037	1000

390 days chosen for assessing primary EP to capture potential events driven by the 360 day FU contact

tct2015 LEADERS FREE

Primary Safety Endpoint

Primary Safety Endpoint*	DCS (n=1221)	BMS (n=1211)
Cardiac Death, Myocardial Infarction, or Stent Thrombosis at 390 days	**112 (9.4%)**	**154 (12.9%)**

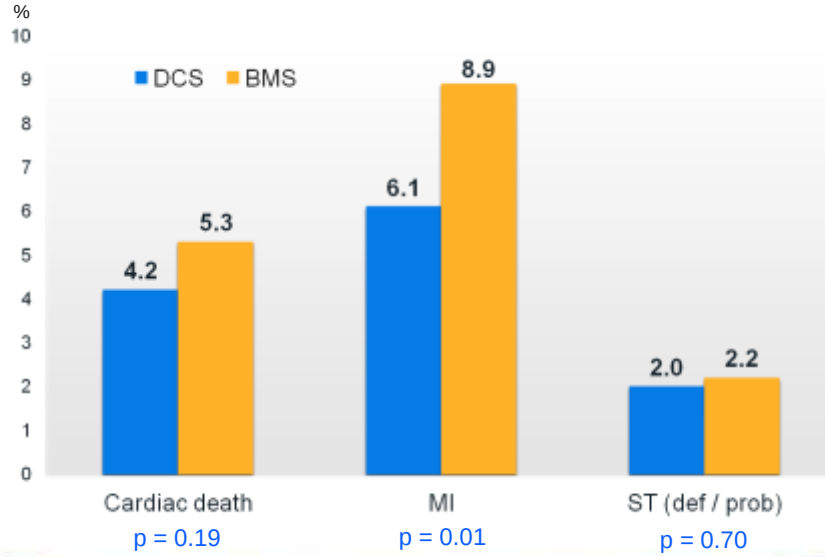
Risk difference:

- -3.6% (95% CI -6.1% to -1.0%)
- HR 0.71, (95% CI = 0.56 – 0.91)
- p < 0.0001 for non-inferiority
- p = 0.005 for superiority

* 3rd Universal definition of MI, Thygesen K et al Circulation 2012;126:2020 –2035
ARC definition, Cutlip D et al. Circulation 2007; 115: 2344-51

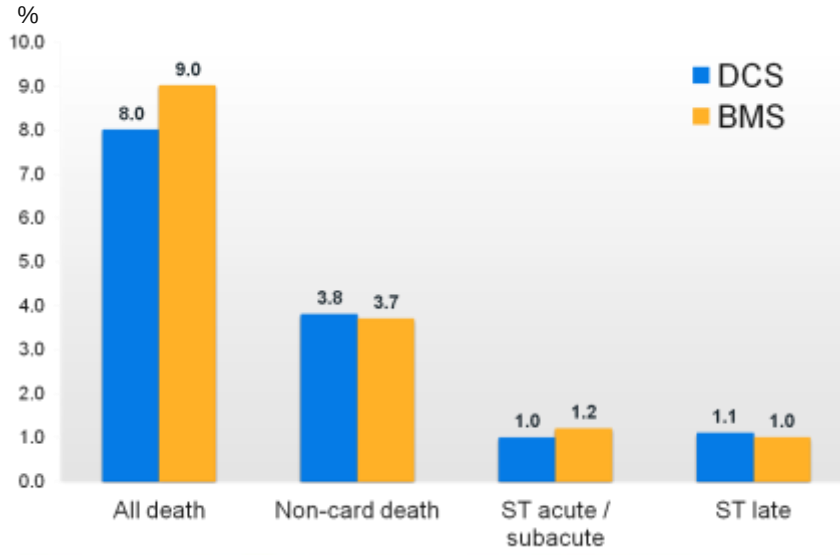
tct2015 LEADERS FREE

Components of Safety Endpoint



tct2015 LEADERS FREE

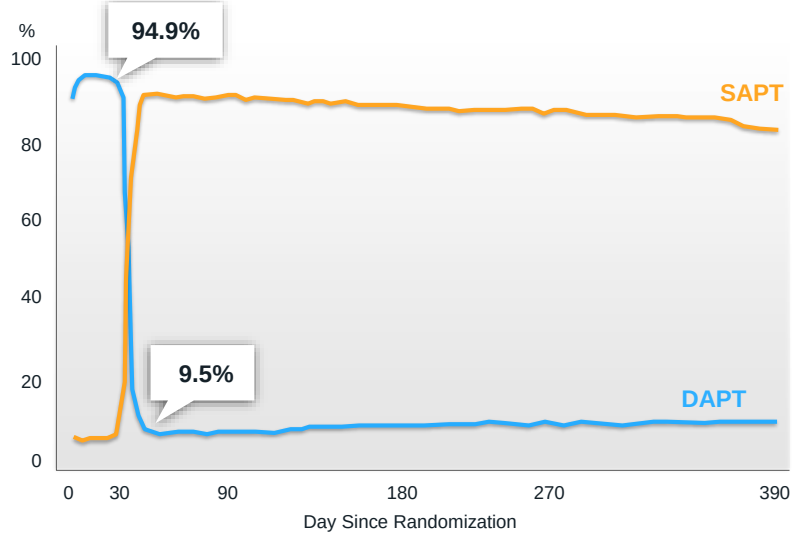
Selected Secondary Safety Endpoints



None of these endpoints differ at p < 0.05

tct2015 LEADERS FREE

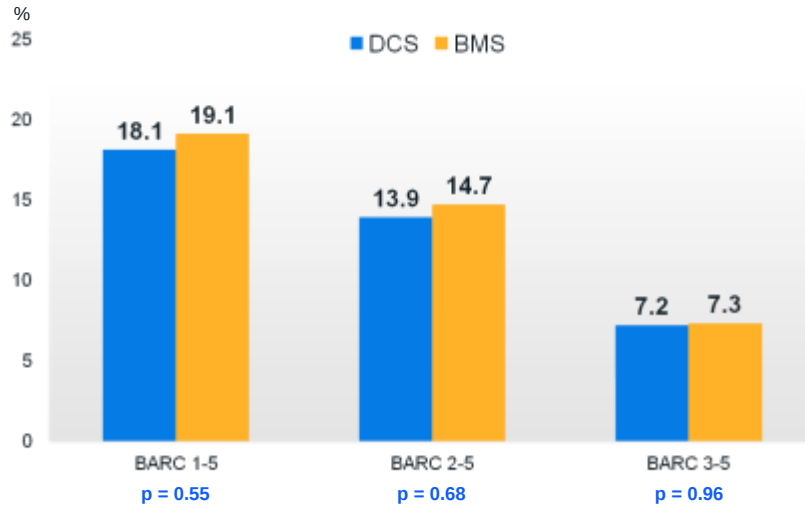
DAPT During Follow-Up



DAPT= dual antiplatelet treatment or clopidogrel alone + vitamin K antagonist during first 30 days

tct2015 LEADERS FREE

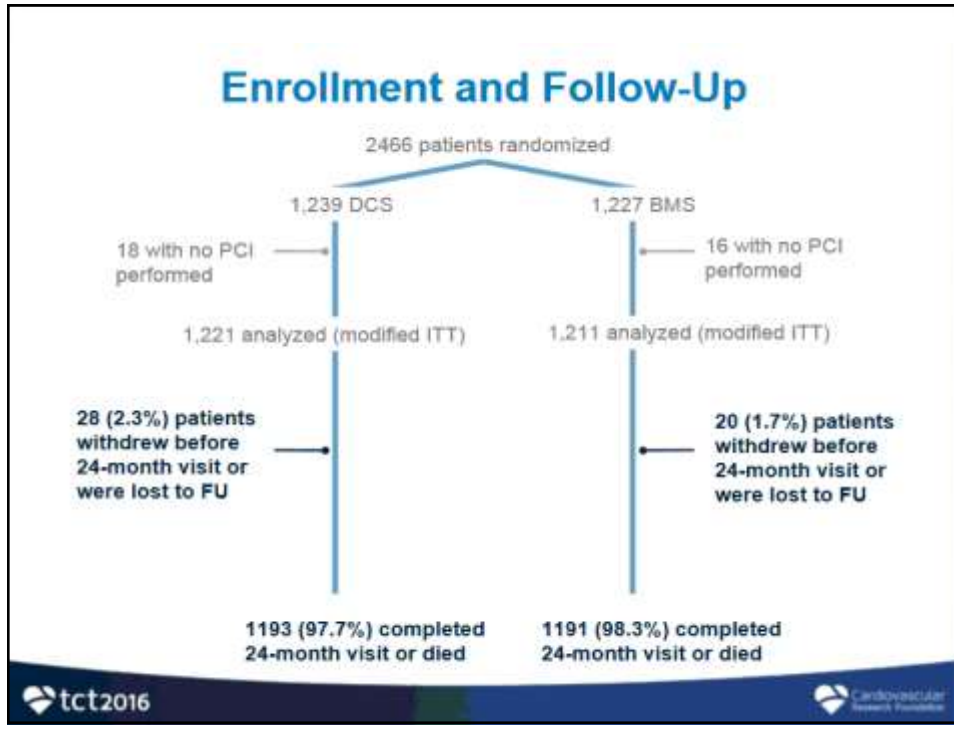
Bleeding During 12 Months Follow-Up

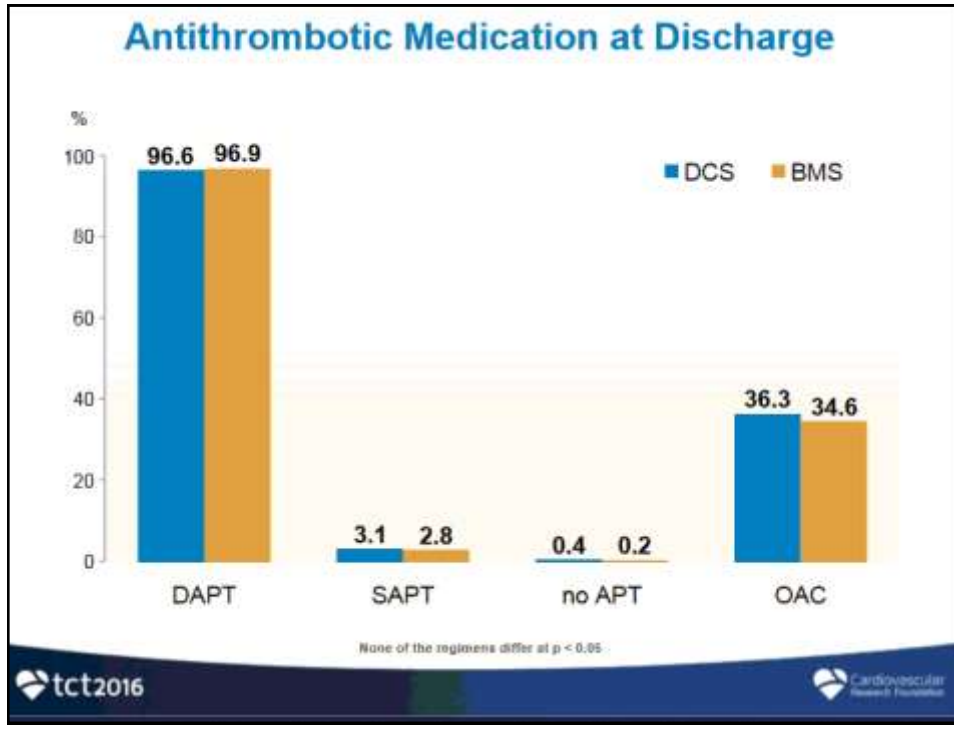


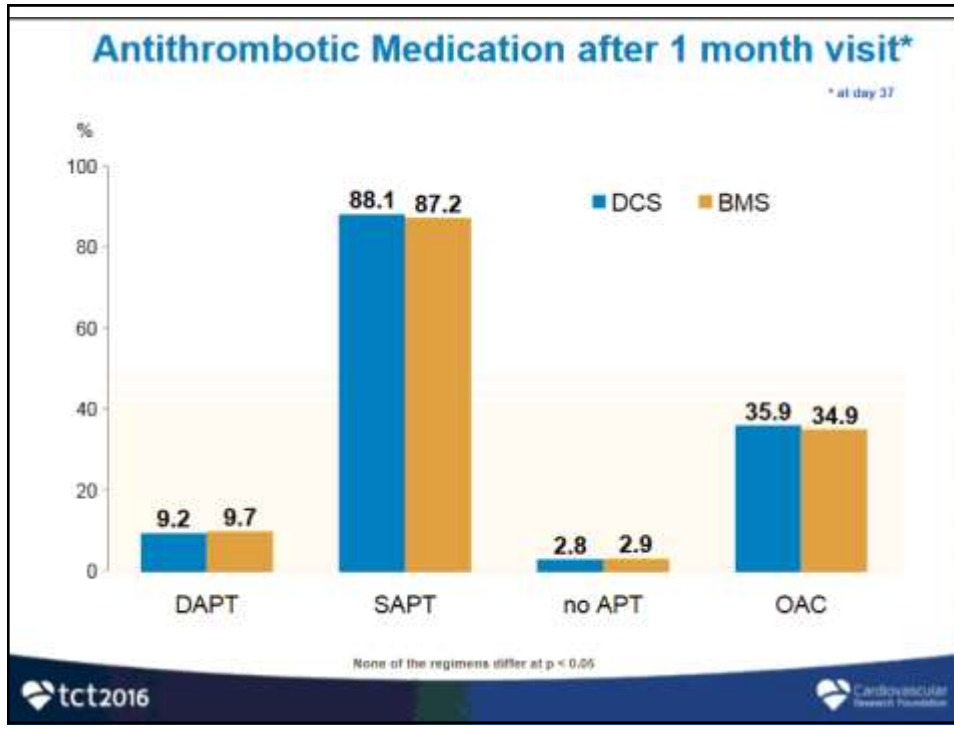
tct2015 LEADERS FREE

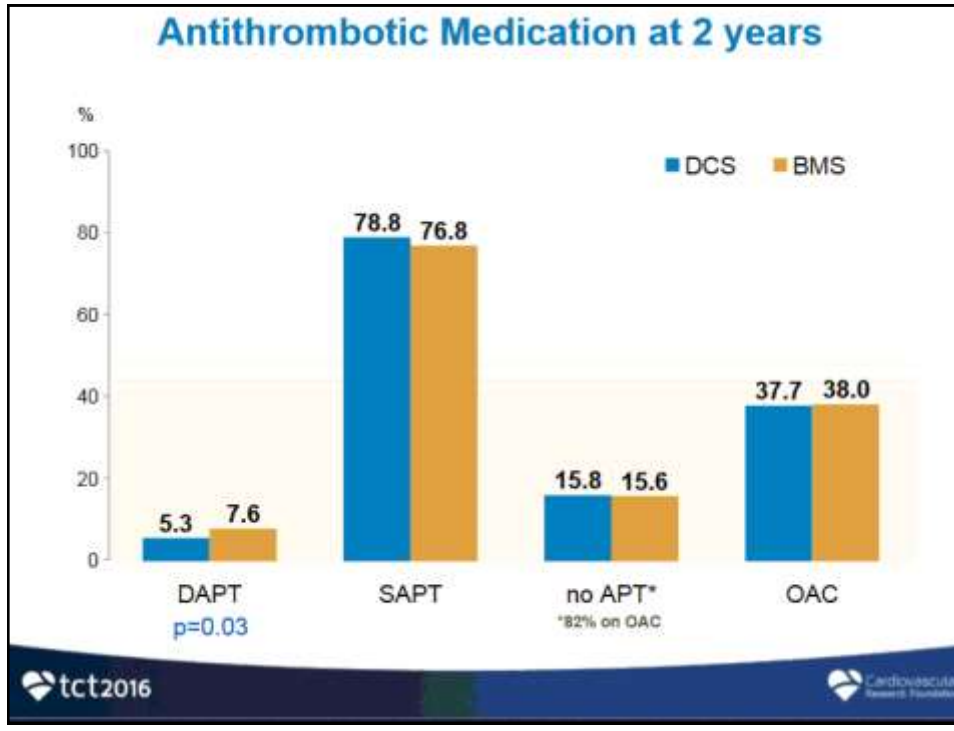
Two Year Follow-up

tct2016 Cardiovascular Research Foundation


Enrollment and Follow-Up
2466 patients randomized
1,239 DCS
1,227 BMS
18 with no PCI performed
16 with no PCI performed
1,221 analyzed (modified ITT)
1,211 analyzed (modified ITT)
28 (2.3%) patients withdrew before 24-month visit or were lost to FU
20 (1.7%) patients withdrew before 24-month visit or were lost to FU
1193 (97.7%) completed 24-month visit or died
1191 (98.3%) completed 24-month visit or died
tct2016


Antithrombotic Medication at Discharge
%
100
80
60
40
20
0
DCS
BMS
96.6
96.9
3.1
2.8
0.4
0.2
36.3
34.6
DAPT
SAPT
no APT
OAC
None of the regimens differ at p < 0.05
tct2016


Antithrombotic Medication after 1 month visit*
* at day 37
%
100
80
60
40
20
0
DCS
BMS
9.2
9.7
88.1
87.2
2.8
2.9
35.9
34.9
DAPT
SAPT
no APT
OAC
None of the regimens differ at p < 0.05
tct2016


Antithrombotic Medication at 2 years
%
100
80
60
40
20
0
DCS
BMS
5.3
7.6
78.8
76.8
15.8
15.6
37.7
38.0
DAPT
p=0.03
SAPT
no APT*
*82% on OAC
OAC
tct2016

Primary Safety Endpoint
(Cardiac Death, MI, ST) at 2 year

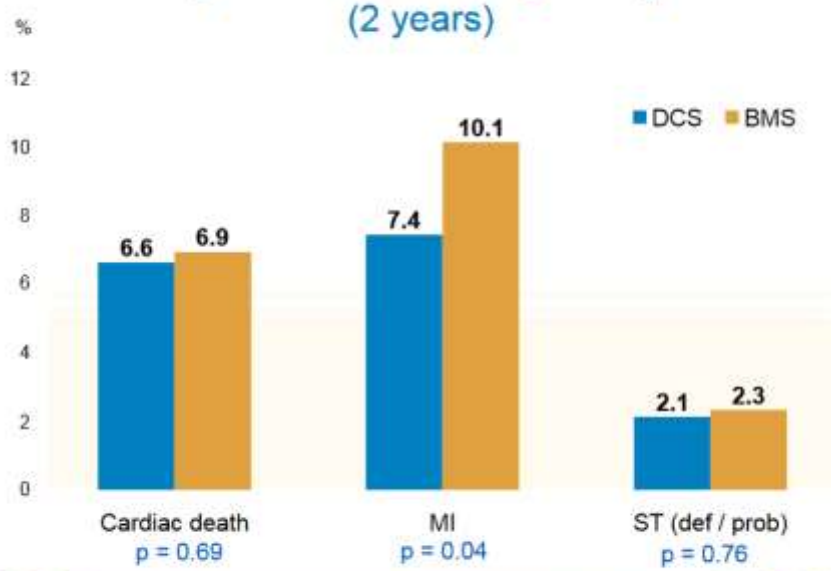
Number at Risk

DCS	1221	1104	1052	1006	620
BMS	1211	1067	1010	973	587

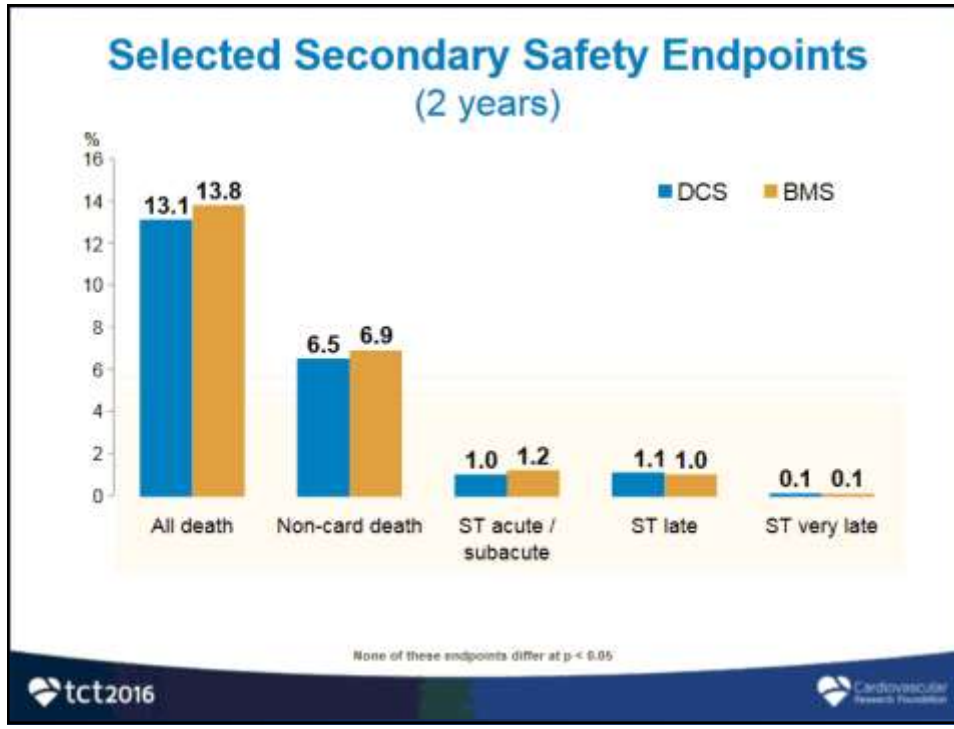
2 year FU was obtained at 730 days ± 60 days

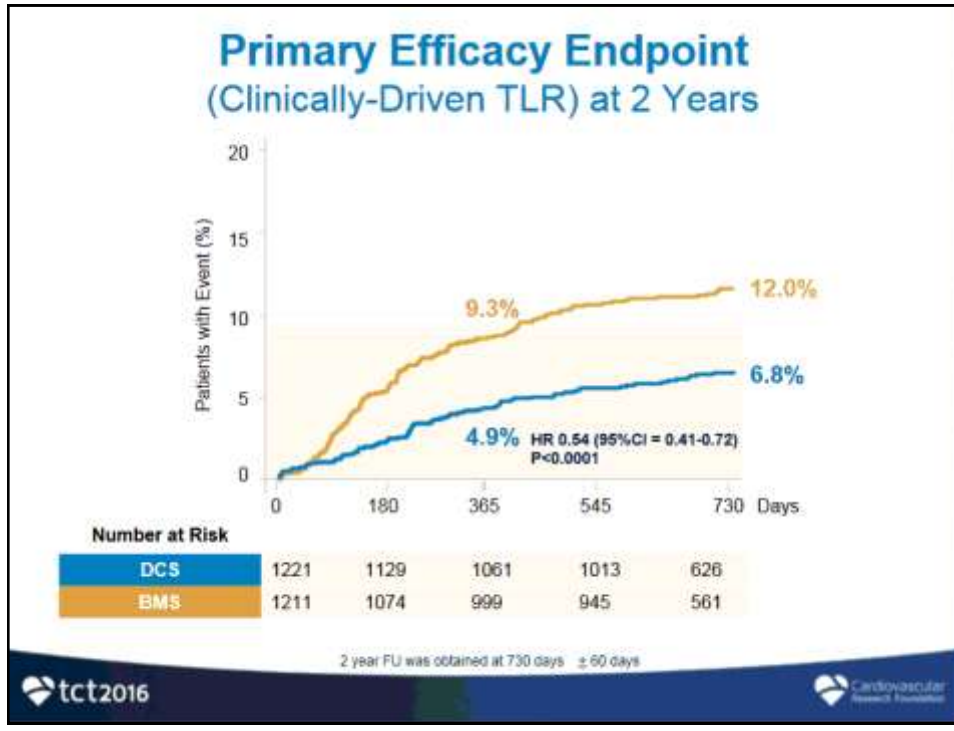
tct2016

Components of Safety Endpoint
(2 years)



tct2016


Selected Secondary Safety Endpoints
(2 years)
%
16
14
12
10
8
6
4
2
0
DCS
BMS
13.1
13.8
6.5
6.9
1.0
1.2
1.1
1.0
0.1
0.1
All death
Non-card death
ST acute / subacute
ST late
ST very late
None of these endpoints differ at p < 0.05
tct2016


Primary Efficacy Endpoint
(Clinically-Driven TLR) at 2 Years
Patients with Event (%)
20
15
10
5
0
9.3%
12.0%
6.8%
4.9%
HR 0.54 (95%CI = 0.41-0.72)
P<0.0001
0
180
365
545
730
Days
Number at Risk
DCS 1221 1129 1061 1013 626
BMS 1211 1074 999 945 561
2 year FU was obtained at 730 days ± 60 days
tct2016

Subgroups at 2 years follow-up

The Balance of Thrombosis and Bleeding

Multivariate Predictors of Primary Safety Endpoint and Major Bleeding (BARC 3-5)

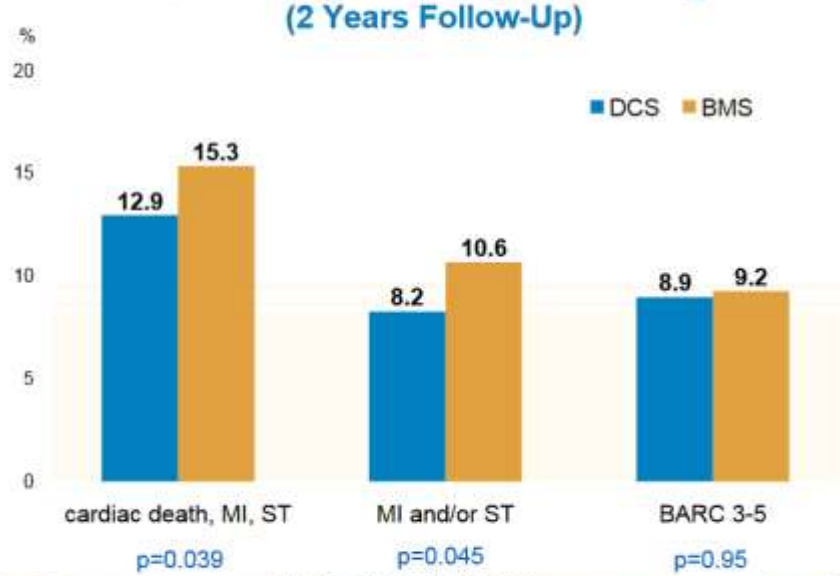
	Cardiac death/MI/ST	Major Bleeding
Congestive heart failure	1.61 (1.23-2.11) p=0.001	
Multivessel disease	1.66 (1.27–2.18) p<0.001	-
Number of stents / patient (per stent)	1.20 (1.09–1.32) p<0.001	-
BMS (vs. DCS)	1.28 (1.03–1.59) p=0.027	-
Age > 75	1.56 (1.23–1.97) p<0.001	1.52 (1.13–2.06) p=0.006
Haemoglobin (per 1 mmol/l lower)*	1.32 (1.19–1.46) p<0.001	1.73 (1.52–1.96) p<0.001
Serum creatinine > 150 umol/l	-	1.58 (1.10–2.27) p=0.012
Planned oral anticoagulants	-	2.01 (1.51–2.68) p<0.001

* Below 9 mmol/l (145 g/l)

tct2016

Cardiovascular Research Foundation

Cardiac, Coronary and Major Bleeding events (2 Years Follow-Up)

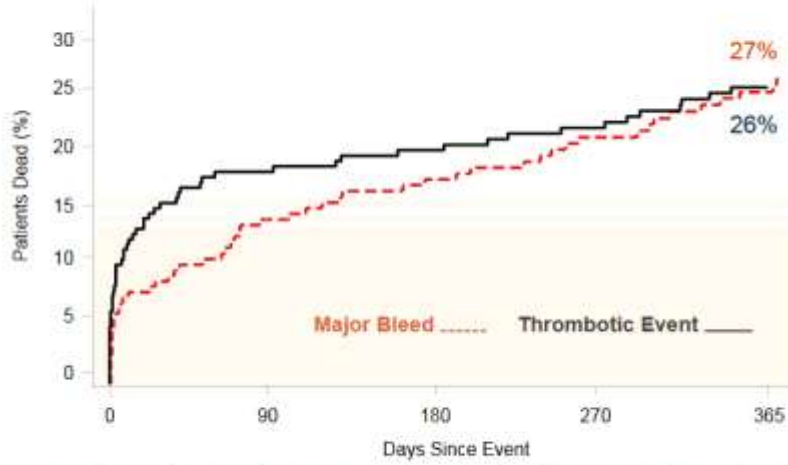


All % derived from Kaplan-Meier estimates

tct2016

Cardiovascular Research Foundation

Mortality During the Year Following a Coronary Thrombotic Event (MI and/or ST) or a Major Bleeding event (BARC 3-5)



1-year mortality = 6% for patients with neither thrombotic nor major bleeding events

tct2016

Conclusions

- At two years, the use of a BA9-DCS remained both significantly safer and more effective than a control BMS in HBR patients treated with a one-month only DAPT course
- No subgroup was identified for which use of a BMS was superior to a DCS
- HBR patients suffer from a persistently high incidence of bleeding and thrombotic events, both of which are associated with a high and similar mortality over a one year period
- Identification of predictors of both the composite primary safety event and major bleeding may help design future trials of DAPT duration for HBR patients

tct2016

THANK YOU