

# **Small Vessel Disease - To Stent or DEB: What Does the Data Show?**

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# Disclosure

- Nothing Significant

# Small Vessel Disease DES Vs DEB

## *Introduction*

- Definition
  - Inconsistent across the trials
  - Different threshold for maximum luminal diameter → 2.25 mm to 3.0 mm
  - An overlapping area as “Large vessel trials” included 2.75 mm onwards as well
  - Definitions discrepancies might have an important impact on various parameters of treatment outcome
- Extent of problem
  - Small vessel CAD is present in 30 to 67% of patients undergoing PCI in different series.
  - More frequent in
    - Female gender
    - Diabetes mellitus
    - Chronic renal failure
    - Specific anatomical subsets like distal segment and bifurcation lesions

# Small Vessel Disease DES Vs DEB

## *Importance of Small vessel*

- Patients undergoing PTCA or CABG
  - Only 30% of patients with lesions in the proximal part show concomitant lesions in the distal vessel as well.
  - The majority pts with small vessel disease have proximal disease
  - Myocardial supply by vessel is not only affected by vessel diameter and length as well
  - True vessel diameter, usually underestimated by CAG and intravascular imaging, may be required for true vessel diameter

# Small Vessel Disease DES Vs DEB

## *Challenges of Intervention in small vessel*

- DES has reduced the in-stent restenosis by 60-75%
- Has challenges when it comes to SvCAD
  - Delayed healing, inflammation and endothelial dysfunction
  - Increased risk of late and very late thrombosis
  - Longer duration of DAPT
- Drug Eluting balloons (DEB)
  - Novel evolving technology
  - Semi-compliant balloon coated with lipophilic antiproliferative drugs
  - Uses less well defined despite the advantage of nothing being left out in the vessel after treatment

# Small Vessel Disease DES Vs DEB

## *Initial Data*

- SCAAR Registry from Sweden
  - 14788 Pts with PCI to small vessel (<2.5 mm) from 2009 to 2017
  - DEB → Increased risk of restenosis Vs DES (adjusted HR 2.027; 95%CI [1.54–2.67])
  - No difference in
    - All-cause deaths (HR 1.178; 95% CI [0.99–1.4])
    - Target lesion thrombosis (HR 0.741; 95% CI [0.41–1.33])
  - Has high risk factor in DEB group
  - No angiographic Follow up
- PICCOLETO Trial(2010)
  - Stopped prematurely
  - High rates of MACE at 9 months with the DIOR balloon.

# Small Vessel Disease DES Vs DEB

*Small vessel vs. large vessel outcome – initial data*

- DUTCH PEERS Trial
  - Resolute Integrity vs Promus Element
  - At least one small coronary vessel (<2.5 mm) vs target lesions in Larger size vessel(>2.5)
  - 2 Yrs follow up
    - TLF (9.5% vs 5.4%, P 1/4 .001)
    - target vessel MI (3.1% vs 1.3%, P 1/4 .006)
    - TLR (4.8% vs 2.8%; P 1/4 .02)
    - higher among patients treated in at least 1 small vessel.
    - patients with a target vessel diameter of <2.25 mm had TLF rates similar to those with a target vessel diameter of 2.25 to <2.50 mm;
    - patients with vessel diameters >2.50 to <3.00 mm and those with vessel diameters of 3.00 mm who underwent treatment had lower TLF rates (9.3%, 9.8%, 5.0%, 5.8%, respectively)

# Small Vessel Disease DES Vs DEB

## Study Characteristics

Table 1: Study Characteristics

	RESTORE SVD (2018) <sup>19</sup>	BELLO (2015) <sup>18</sup>	PICCOLETO 2 (2020) <sup>17</sup>	BASKET-SMALL 2 (2018) <sup>16</sup>
DEB/type	n=116 Paclitaxel-coated balloon (RESTORE SVD)	n=90 Paclitaxel-coated balloon (Inpact Falcon)	n=108 Elutax SV	n=382 Paclitaxel-coated balloon (SeQuent Please)
DES/type	n=114 Zotarolimus-eluting stent (Resolute) Second generation	n=92 First-generation paclitaxel-eluting stent (TAXUS Liberté)	n=106 XIENCE EES	n=376 Second-generation paclitaxel-eluting stent or everolimus-eluting stent (XIENCE)
Small vessel definition	<2.75 mm	<2.8 mm	<2.75 mm	<3 mm
MACE definition	NA	Death, MI, TVR	Cardiac death, MI, TLR	Death, non-fatal MI, TVR
Duration of follow-up	36 months	24 months	12 months	36 months

DEB = drug-eluting balloon; DES = drug-eluting stent; MACE = major adverse cardiac events; NA = not available; TLR = target lesion revascularisation; TVR = target vessel revascularisation.



# Small Vessel Disease DES Vs DEB

## Patients Characteristics

	RESTORE SVD (2018) <sup>19</sup>		BELLO (2015) <sup>18</sup>		PICCOLETO 2 (2020) <sup>17</sup>		BASKET-SMALL 2 (2018) <sup>16</sup>	
	DEB	DES	DEB	DES	DEB	DES	DEB	DES
Mean age (years)	60.1 (SD 10.5)	60.5 (SD 10.8)	64.8 (SD 8.5)	66.4 (SD 9)	64 (IQR 48–80)	66 (IQR 50–82)	67.2 (SD 10.3)	68.4 (SD 10.3)
Man	77 (66.4%)	88 (77.2%)	80 (72%)	71 (77.2%)	83 (70.3%)	87 (76.9%)	295 (77%)	262 (70%)
Current smoker	34 (29.3%)	36 (31.6%)	15 (16.7%)	10 (10.9%)	23% (19.5)	19% (16.7)	22% (82)	20% (72)
Dyslipidaemia	61 (52.6%)	55 (48.2%)	71 (78.9%)	73 (79.3%)	61 (72%)	55 (63%)	262 (69%)	259 (70%)
Hypertension	78 (67.2%)	86 (75.4%)	80 (72%)	75 (81.5%)	77 (65.2%)	67.2 (76%)	324 (85%)	332 (89%)
Diabetes	46 (39.7%)	48 (42.1%)	43.3 (39%)	38 (35%)	38 (45%)	35.5 (40%)	122 (32%)	130 (35%)
Previous MI	26 (22.4%)	28 (24.6%)	46 (51.1%)	33 (35.9%)	38 (45%)	30 (34%)	160 (42%)	133 (35%)
Previous PCI	45 (38.8%)	38 (33.3%)	52 (57.8%)	39 (42.4%)	50 (59%)	53 (60%)	235 (62%)	241 (64%)

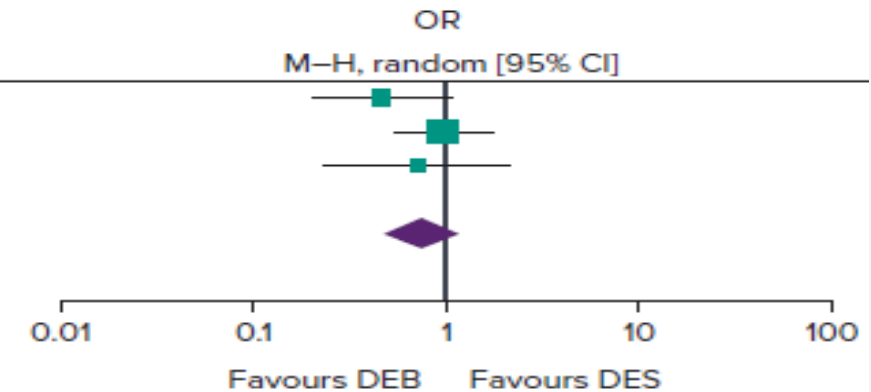
DEB = drug-eluting balloon; DES = drug-eluting stent; IQR = interquartile ratio; PCI = percutaneous coronary intervention.

# Small Vessel Disease DES Vs DEB

## Major Adverse Cardiac Events

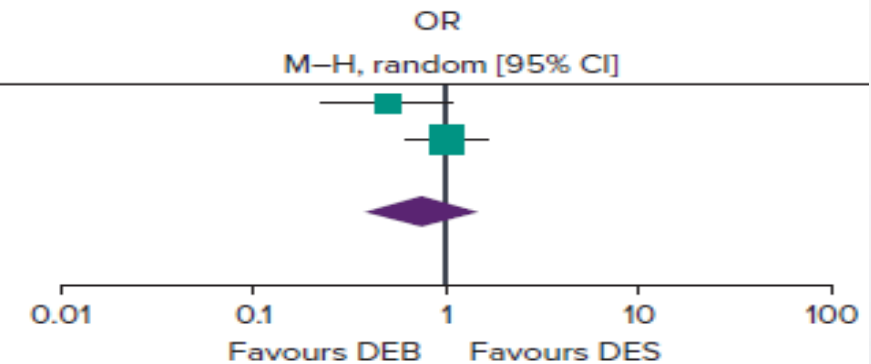
One year

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BELLO, 2015 <sup>18</sup>	11	90	21	92	28.9%	0.47 [0.21–1.04]
BASKET-SMALL 2, 2020 <sup>16</sup>	28	382	28	376	55.0%	0.98 [0.57–1.69]
PICCOLETO, 2020 <sup>17</sup>	6	108	8	106	16.1%	0.72 [0.24–2.15]
Total [95% CI]		580		574	100.0%	0.76 [0.48–1.19]
Total events	45		57			
Heterogeneity: $\tau^2=0.02$ ; $\chi^2=2.25$ , d.f.=2 (p=0.32); $I^2=11\%$						
Test for overall effect: Z=1.21 (p=0.23)						



Two years

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BELLO, 2015 <sup>18</sup>	13	90	23	92	40.1%	0.51 [0.24–1.08]
BASKET-SMALL 2, 2020 <sup>16</sup>	42	382	41	376	59.9%	1.01 [0.64–1.59]
Total [95% CI]		472		468	100.0%	0.77 [0.39–1.48]
Total events	55		64			
Heterogeneity: $\tau^2=0.14$ ; $\chi^2=2.35$ , d.f.=1 (p=0.12); $I^2=58\%$						
Test for overall effect: Z=0.79 (p=0.43)						



DEB = drug-eluting balloon; DES = drug-eluting stent; MACE = major adverse cardiac events; M-H = Mantel-Haenszel.

# Small Vessel Disease DES Vs DEB

## *Major Adverse Cardiac Events*

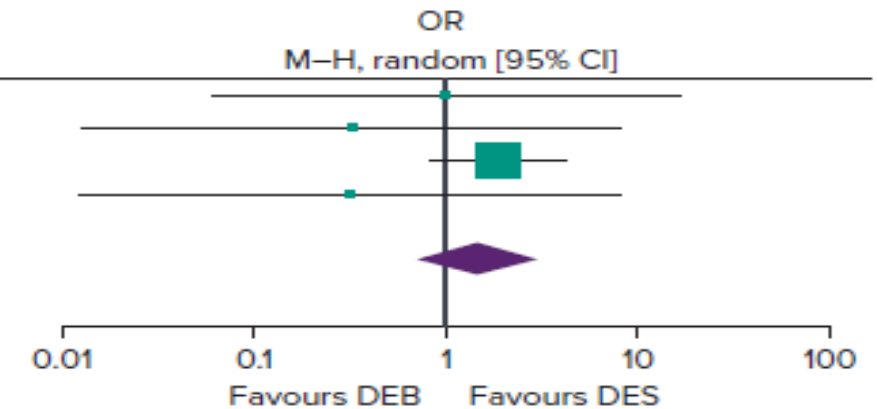
- MACE
- At 1 year 1154 participants
  - No significant difference between the two arms (OR 0.76; 95% CI [0.48–1.19]);
- At 2 years, 940 participants
  - No significant difference (OR 0.77; 95% CI [0.39–1.48]).
- BASKET-SMALL 2 reported 3-year data
  - No statistical difference (OR 0.98; 95% CI [0.65–1.48])

# Small Vessel Disease DES Vs DEB

## All-Cause Mortality – 1 Year

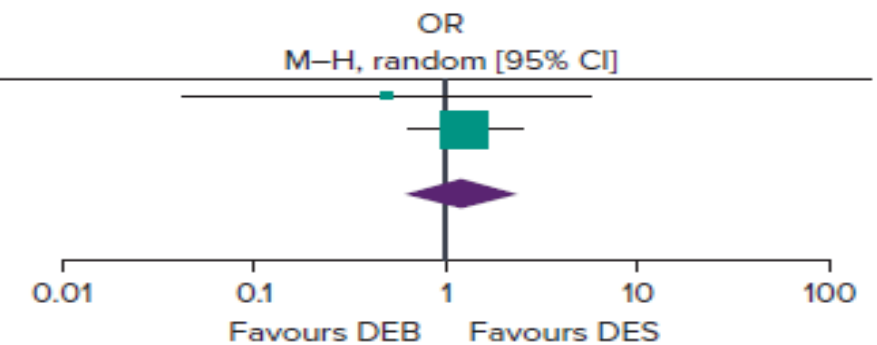
One year

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BELLO, 2015 <sup>18</sup>	1	90	1	92	7.1%	1.02 [0.06–16.60]
RESTORE SVD, 2018 <sup>19</sup>	0	114	1	114	5.4%	0.33 [0.01–8.20]
BASKET-SMALL 2, 2020 <sup>16</sup>	17	382	9	376	82.1%	1.90 [0.84–4.32]
PICCOLETO, 2020 <sup>17</sup>	0	108	1	106	5.4%	0.32 [0.01–8.05]
Total [95% CI]		694		688	100.0%	1.50 [0.72–3.17]
Total events	18		12			
Heterogeneity: $\tau^2 = 0.00$ ; $\tau^2 = 2.12$ , d.f.=3 (p=0.55); $I^2 = 0\%$						
Test for overall effect: Z=1.08 (p=0.28)						



Two years

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BELLO, 2015 <sup>18</sup>	1	90	2	92	6.7%	0.51 [0.05–5.68]
BASKET-SMALL 2, 2020 <sup>16</sup>	22	382	17	376	93.3%	1.29 [0.67–2.47]
Total [95% CI]		472		468	100.0%	1.21 [0.65–2.27]
Total events	23		19			
Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 0.54$ , d.f.=1 (p=0.46); $I^2 = 0\%$						
Test for overall effect: Z=0.60 (p=0.55)						



DEB = drug-eluting balloon; DES = drug-eluting stent; M-H = Mantel-Haenszel.

# Small Vessel Disease DES Vs DEB

*All Cause Mortality*

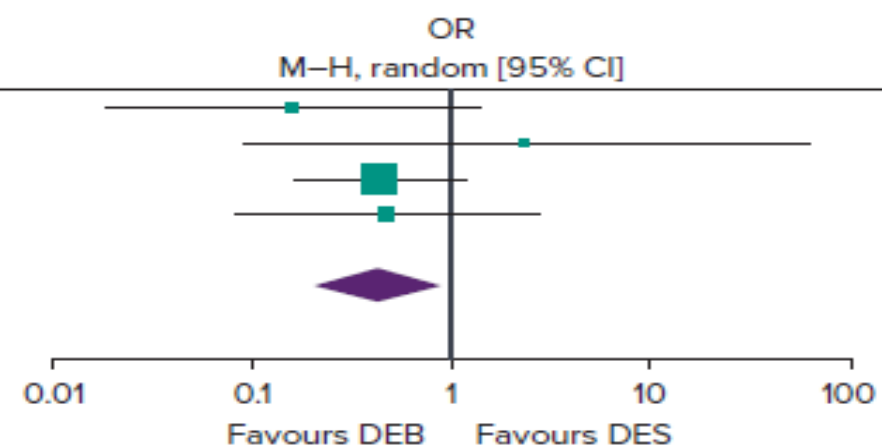
- At 1 year in all four RCTs
  - no significant difference between DEBs and DESs (OR 1.50; 95% CI [0.72–3.17]);
- At two-year data available for BELLO and BASKET-SMALL 2
  - No significant difference (OR 1.21; 95% CI [0.65–2.27])
- Three-year data were available for RESTORE SVD
  - NO difference (OR 1.02; 95% CI [0.59–1.77]).

# Small Vessel Disease DES Vs DEB

## Myocardial Infarction Rate – 1 Year

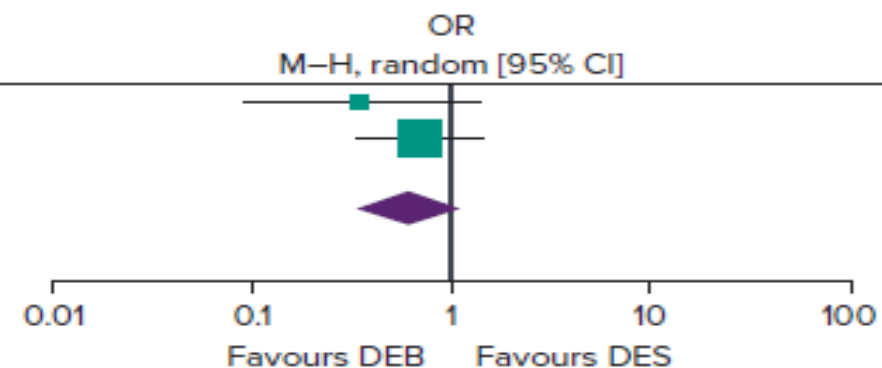
One year

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BELLO, 2015 <sup>18</sup>	1	90	6	92	12.9%	0.16 [0.02–1.37]
RESTORE SVD, 2018 <sup>19</sup>	1	146	0	114	5.7%	2.36 [0.10–58.50]
BASKET-SMALL 2, 2020 <sup>16</sup>	6	382	13	376	61.5%	0.45 [0.17–1.18]
PICCOLETO, 2020 <sup>17</sup>	2	108	4	106	19.9%	0.48 [0.09–2.68]
Total [95% CI]		726		688	100.0%	0.44 [0.20, 0.94]
Total events	10		23			
Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 1.92$ , d.f.=3 (p=0.59); $I^2 = 0\%$						
Test for overall effect: Z=2.12 (p=0.03)						



Two years

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BELLO, 2015 <sup>18</sup>	3	90	8	92	21.2%	0.36 [0.09–1.41]
BASKET-SMALL 2, 2020 <sup>16</sup>	14	382	19	376	78.8%	0.71 [0.35–1.45]
Total [95% CI]		472		468	100.0%	0.62 [0.33–1.16]
Total events	17		27			
Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 0.76$ , d.f.=1 (p=0.38); $I^2 = 0\%$						
Test for overall effect: Z=1.50 (p=0.13)						



DEB = drug-eluting balloon; DES = drug-eluting stent; M-H = Mantel-Haenszel.

# Small Vessel Disease DES Vs DEB

*Myocardial Infarction Rate – 1 Year*

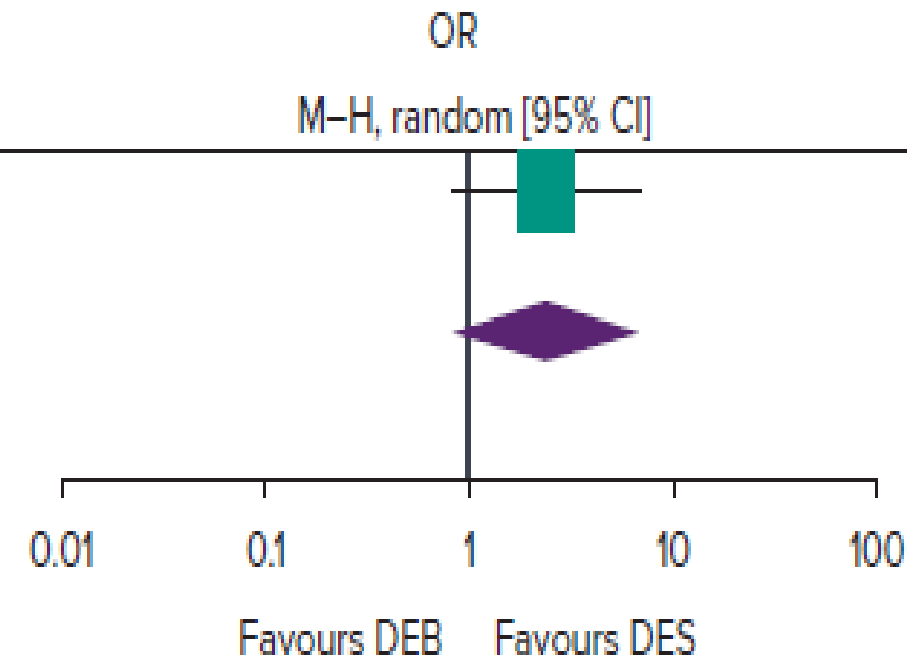
- All four RCTs at 1 year
  - Indicating a significant reduction in MI for the DEB arm at 1 year (OR 0.44; 95% CI [0.2–0.94])
  - On sensitivity analysis, the difference became more significant if both RESTORE SVD and PICCOLETO 2 were removed from the analysis (OR 0.37; 95% CI [0.15–0.91])
  - Becomes non-significant when BELLO and BASKET-SMALL 2 were removed (OR 0.69; 95% CI [0.15–3.12])
- Two years data
  - BASKET-SMALL 2 and BELLO, indicating no significant difference (OR 0.62; 95% CI [0.33–1.16]),
- Three years data
  - BASKET-SMALL 2 recorded 3-year MI data with no significant difference (OR 0.8; 95% CI [0.43–1.5])

# Small Vessel Disease DES Vs DEB

Cardiac Death. 1 Year

One year

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BASKET-SMALL 2, 2020 <sup>16</sup>	12	382	5	376	100.0%	2.41 [0.84-6.90]
Total [95% CI]		382		376	100.0%	2.41 [0.84-6.90]
Total events	12		5			
Heterogeneity: Not applicable						
Test for overall effect: Z=1.63 (p=0.10)						



B = drug-eluting balloon; DES = drug-eluting stent; M-H = Mantel-Haenszel.



# Small Vessel Disease DES Vs DEB

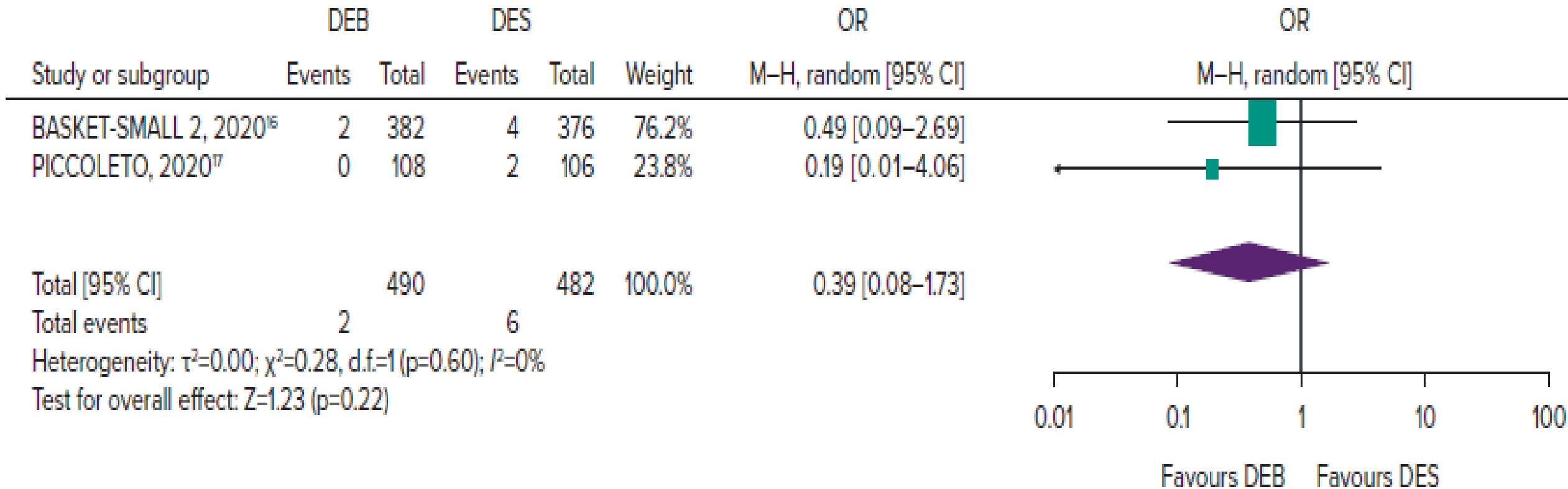
*Cardiac Death. 1 Year*

- At 1 year no cardiac deaths occurred in any arms of the BELLO, RESTORE SVD or PICCOLETO trials.
- BASKET-SMALL 2
  - demonstrated events in both arms at 1 year (OR 2.41; 95% CI [0.84–6.9]),
  - 2 years (OR 1.55; 95% CI [0.66–3.63]) and 3 years (OR 1.3; 95% CI [0.62–2.72])
  - No significant differences were found between the two study arms regardless of follow-up duration

# Small Vessel Disease DES Vs DEB

## Vessel Thrombosis – 1 Year

One year



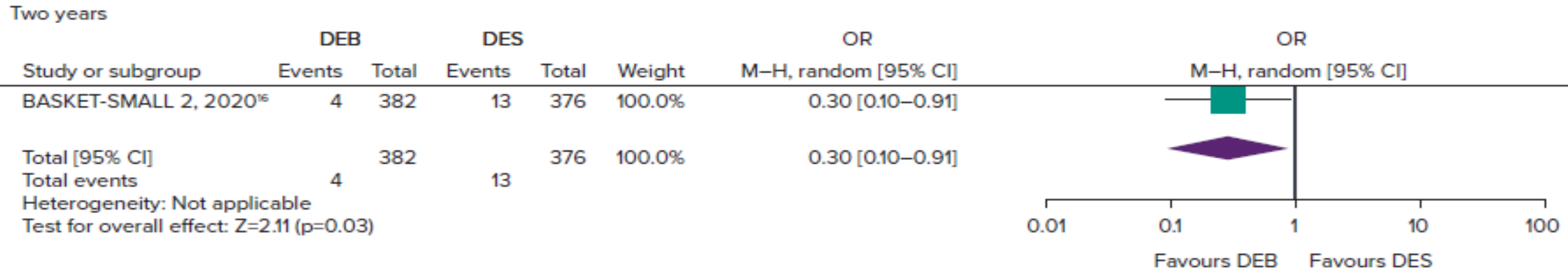
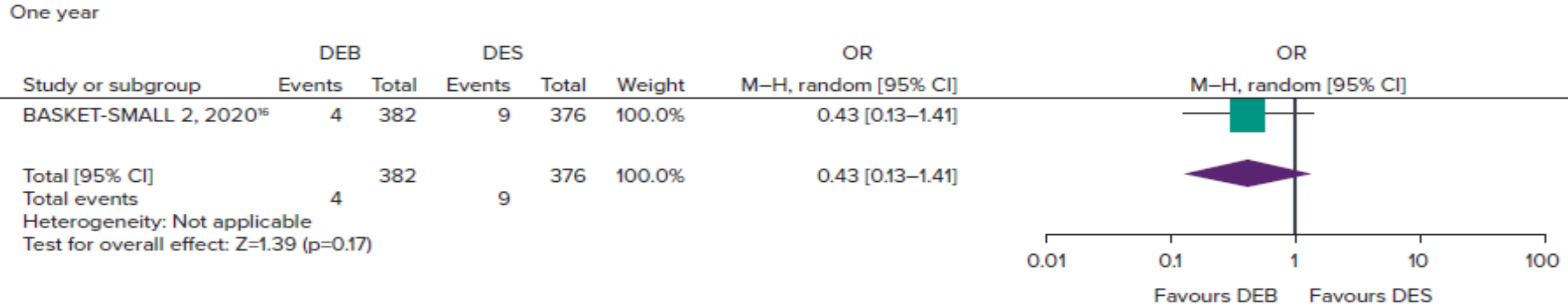
# Small Vessel Disease DES Vs DEB

Vessel Thrombosis – 1 Year

- Recorded in BELLO and BASKET-SMALL 2 at 1 year (1,232 participants), indicating no statistically significant differences between the two arms (OR 0.39, 95% CI [0.09–1.73]);
- BASKET-SMALL 2 further recorded data at 2 years (OR 0.32; 95% CI [0.07–1.62]) with no significant differences
- BASKET-SMALL 2 -- > 3 years (OR 0.32; 95% CI [0.07–1.62]), with no significant differences.

# Small Vessel Disease DES Vs DEB

## Major Bleeding – 1 Year



DEB = drug-eluting balloon; DES = drug-eluting stent; M-H = Mantel-Haenszel.

# Small Vessel Disease DES Vs DEB

## *Major Bleeding*

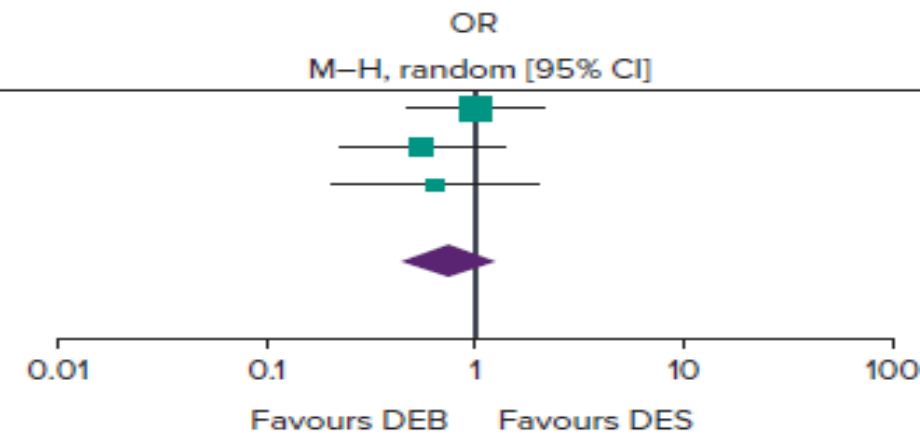
- The PICCOLETO 2 and BASKET-SMALL 2 trials recorded data for 1 year
  - PICCOLETO 2 recorded no events at 1 year
  - BASKET-SMALL 2 reported no significant difference between the arms (OR 0.43; 95% CI [0.13–1.41]).
  - The 2- and 3-year follow-up data
    - BASKET-SMALL 2, with a statistically significant reduction in the odds of major bleeding at 2 years (OR 0.3; 95% CI [0.1–0.91]),
    - with no difference at 3 years and a trend towards the DEB arm (OR 0.41; 95% CI [0.16–1.09]).

# Small Vessel Disease DES Vs DEB

## Target Vessel Revascularization

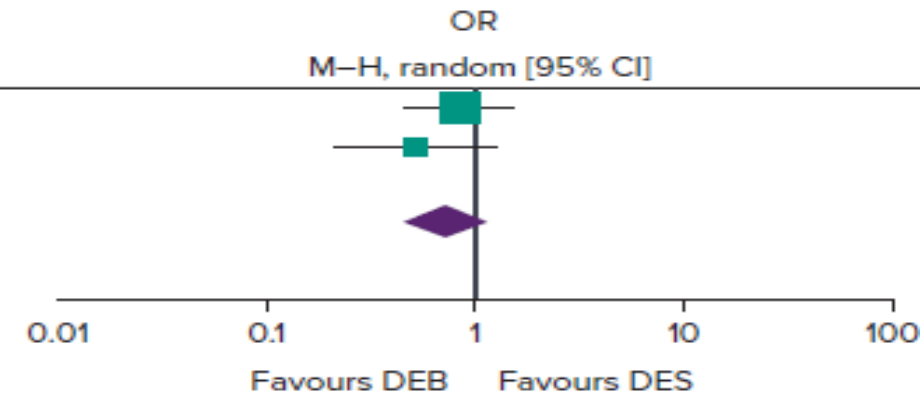
One year

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BASKET-SMALL 2 2020 <sup>16</sup>	13	282	17	376	46.8%	1.02 [0.49–2.14]
BELLO 2015 <sup>18</sup>	9	90	15	92	32.8%	0.57 [0.24–1.38]
RESTORE SVD 2018 <sup>19</sup>	6	146	7	114	20.4%	0.66 [0.21–2.01]
Total [95% CI]		518		582	100.0%	0.77 [0.46–1.28]
Total events	28		39			
Heterogeneity: $\tau^2=0.00$ ; $\chi^2=1.08$ , d.f.=2 (p=0.58); $I^2=0\%$						
Test for overall effect: Z=1.01 (p=0.31)						



Two years

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BASKET-SMALL 2 2020 <sup>16</sup>	23	382	26	376	69.5%	0.86 [0.48–1.54]
BELLO 2015 <sup>18</sup>	9	90	16	92	30.5%	0.53 [0.22–1.27]
Total [95% CI]		472		468	100.0%	0.74 [0.46–1.20]
Total events	32		42			
Heterogeneity: $\tau^2=0.00$ ; $\chi^2=0.84$ , d.f.=1 (p=0.36); $I^2=0\%$						
Test for overall effect: Z=1.21 (p=0.23)						



DEB = drug-eluting balloon; DES = drug-eluting stent; M-H = Mantel-Haenszel; TVR = target vessel revascularisation.

# Small Vessel Disease DES Vs DEB

## *Target Vessel Revascularization*

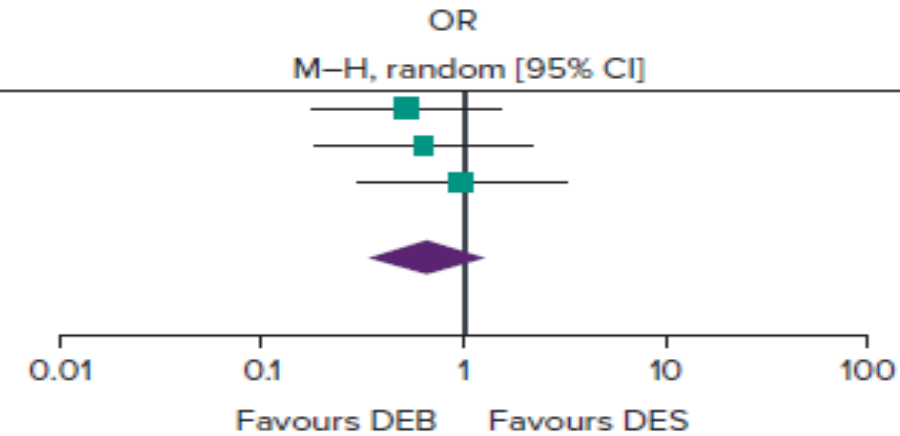
- RESTORE SVD, BELLO and PICCOLETO 2
  - Target vessel revascularisation (TVR) for 1,100 participants at 1 year of follow-up
    - TVR rates indicated no difference at 1 year (OR 0.77; 95% CI [0.46–1.28]).
  - The 2-year data were presented for BELLO and BASKET-SMALL 2 (OR 0.74; 95% CI [0.46–1.2]) with no significant difference.
  - 3-year data for BASKET-SMALL 2 (OR 0.92; 95% CI [0.54–1.54]), with no significant difference.

# Small Vessel Disease DES Vs DEB

## Target lesion revascularization

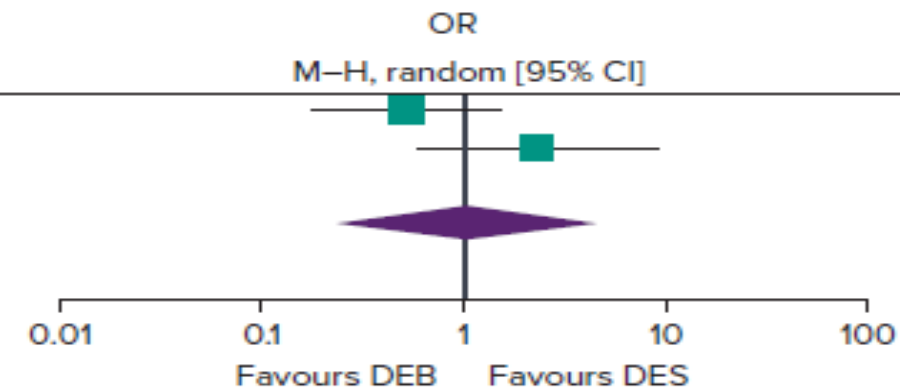
One year

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BELLO, 2015 <sup>18</sup>	6	90	11	92	39.5%	0.53 [0.19–1.49]
RESTORE SVD, 2018 <sup>19</sup>	5	146	6	114	29.0%	0.64 [0.19–2.15]
PICCOLETO, 2020 <sup>17</sup>	6	108	6	106	31.5%	0.98 [0.31–3.14]
Total [95% CI]		344		312	100.0%	0.68 [0.35–1.30]
Total events	17		23			
Heterogeneity: $\tau^2=0.00$ ; $\chi^2=0.62$ , d.f.=2 (p=0.73); $I^2=0\%$						
Test for overall effect: Z=1.17 (p=0.24)						



Two years

Study or subgroup	DEB		DES		Weight	OR M-H, random [95% CI]
	Events	Total	Events	Total		
BELLO, 2015 <sup>18</sup>	6	90	11	92	54.4%	0.53 [0.19–1.49]
RESTORE SVD, 2018 <sup>19</sup>	8	136	3	114	45.6%	2.31 [0.60–8.93]
Total [95% CI]		226		206	100.0%	1.03 [0.24–4.39]
Total events	14		14			
Heterogeneity: $\tau^2=0.72$ ; $\chi^2=2.90$ , d.f.=1 (p=0.09); $I^2=66\%$						
Test for overall effect: Z=0.04 (p=0.96)						





# Small Vessel Disease DES Vs DEB

*Target lesion revascularization*

- TLR at 1 year was available for BELLO, RESTORE SVD and PICCOLETO 2
  - No significant difference between the two study arms (OR 0.68; 95% CI [0.35–1.30]);
- TLR at 2 years is available for RESTORE SVD and BELLO
  - non-significant 2-year outcomes (OR 1.03; 95% CI [0.24–4.39]).
- TLR at 3 years is available for RESTORE
  - with no significant difference (OR 2.55; 95% CI [0.67–9.65])

# Conclusion

- Long-term follow-up of DEB and DES use in small coronary arteries demonstrates DEBs to be comparable with DESs
- DEBs demonstrated significantly reduced rates of non-fatal MI at 1 year,
- BASKET-SMALL 2 trials demonstrated significantly reduced rates of bleeding at 2 years
- The sustained performance of DEBs over 3 years of follow-up demonstrates the role of DEBs in treating small coronary artery disease
- DEB is one of the viable and strong alternatives for small vessel intervention