Meta-Analysis of Randomized Clinical Trials Comparing Biodegradable Polymer Drug-Eluting Stent to Second -Generation Durable Polymer Drug-Eluting Stents

El-Hayek G, et al. JACC Cardiovasc Interv. 2017 Mar 13;10(5):462-473.

OBJECTIVES The authors sought to perform a meta-analysis of randomized clinical trials (RCTs) comparing the safety and efficacy of biodegradable polymer drug-eluting stents (BP-DES) to second-generation durable polymer drug-eluting stents (DP-DES).

BACKGROUND Prior meta-analyses have established the superiority of BP-DES over bare-metal stents and first-generation DP-DES; however, their advantage compared with second-generation DP-DES remains controversial.

METHODS The authors searched PubMed and Scopus databases for RCTs comparing BP-DES to the second-generation DP-DES. Outcomes included target vessel revascularization (TVR) as efficacy outcome and cardiac death, myocardial infarction (MI), and definite or probable stent thrombosis (ST) as safety outcomes. In addition, we performed landmark analysis for endpoints beyond 1 year of follow-up and a subgroup analysis based on the stent characteristics.

RESULTS The authors included 16 RCTs comprising 19,886 patients in the meta-analysis. At the longest available follow-up (mean duration 26 months), we observed no significant differences in TVR ($p = 0.62$), cardiac death ($p = 0.46$), MI ($p = 0.98$), or ST (risk ratio: 0.83, 95% confidence interval: 0.64 to 1.09; $p = 0.19$). Our landmark analysis showed that BP-DES were not associated with a reduction in the risk of very late ST (risk ratio: 0.87, 95% confidence interval: 0.49 to 1.53; $p = 0.62$). Similar outcomes were seen regardless of the eluting drug (biolimus vs. sirolimus), the stent platform (stainless steel vs. alloy), the kinetics of polymer degradation or drug release (<6 months vs. >6 months), the strut thickness of the BP-DES (thin <100 μm vs. thick >100 μm), or the DAPT duration (≥ 6 months vs. ≥ 12 months).

CONCLUSIONS BP-DES have similar safety and efficacy profiles to second-generation DP-DES.

生物可降解性聚合物塗層的藥物釋放支架 (Biodegradable Polymer Drug-Eluting Stent) 與第二代耐久性聚合物塗層的藥物釋放支架 (Second-Generation Durable Polymer Drug-Eluting Stent) 相比較之隨機臨床研究綜合薈萃分析

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緣由

冠狀動脈支架近年來已經成為冠狀動脈心臟病的主要治療之一。先以冠狀動脈氣球擴張術擴張並撐開冠狀動脈硬化斑塊，然後植入支架，以維持血液暢通。藥物釋放支架晚期血栓發生率的議題，引發臨床醫師對於聚合物 (Polymer) 存在及安全性的關注。

已有綜合薈萃分析顯示，生物可降解性聚合物塗層的藥物釋放支架 (Biodegradable Polymer Drug-Eluting Stent, BP-DES)，要優於裸金屬支架 (Bare-Metal Stent, BMS) 及第一代耐久性聚合物塗層的藥物釋放支架 (Durable Polymer Drug-Eluting Stent, DP-DES)。但 BP-DES 是否也優於第二代 DP-DES 則未有定論。

本研究想藉由隨機臨床研究作綜合薈萃分析，試圖回答生物可降解性聚合物塗層藥物釋放支架 (BP-DES) 與第二代耐久性聚合物塗層藥物釋放支架 (DP-DES) 兩者在安全性及有效性的比較。

方法

使用 Pubmed 及 Scopus 資料庫，針對 BP-DES 與第二代 DP-DES 比較的隨機研究作文獻搜尋。以標的血管再治療率 (target vessel revascularization, TVR) 做為有效性目標。以心臟相關死亡，心肌梗塞，及明確或可能支架內血栓做為安全性目標。針對追蹤 1 年以上進行界標分析 (landmark analysis) 並根據支架特性做次族群分析。

結果

此綜合薈萃分析共引入 16 篇隨機臨床研究文獻，共 19886 位病患 (其中 10859 位病患接受 BP-DES，9027 位病患接受第二代 DP-DES)。平均追蹤 26 個月。文獻搜尋策略如圖一及兩組臨床參數如表一。其中標的血管再治療率 (TVR)(p=0.62)，心臟相關死亡 (p=0.46)，心肌梗塞 (p=0.98)，及明確或可能支架內血栓 (risk ratio=0.83, 95% confidence interval: 0.64 to 1.09; p=0.19) 皆未達統計上顯著差異 (中長期追蹤資料如圖二～圖五)。界標分析顯示追蹤超過 1 年，BP-DES 並未降低非常晚期支架內血栓風險 (risk ratio: 0.87, 95% confidence interval: 0.49 to 1.53; p=0.62)(如圖六)。次族群分析則顯示這樣的結論無關於支架上覆載的藥物 (biolimus 或 sirolimus)，支架材質 (不銹鋼或合金)，聚合物降解或藥物釋放動力學 (<6 個月或 >6 個月)，支架厚度 (薄 <100μm 或厚 >100μm)，或使用雙重抗血小板藥物時間 (dual anti-platelet therapy, DAPT) (≥ 6 月或≥ 12 月) (如表二，圖七及圖八)。

討論

支架作為支撐力的平台，避免急性回縮，應該完全內皮化以防止支架內血栓的形成，同時降低血管新生內膜的增生程度。DP-DES 採用不可降解聚合物控制藥物釋放，釋放後長期存在。DES 晚期血栓的發生率略高於裸金屬支架，藥物釋放完成後殘留的聚合物 (Polymer) 有可能是增加晚期血栓形成及不良組織反應的主要原因之一。

生物可降解性聚合物塗層的藥物釋放支架 (BP-DES)，藥物完全釋放後局部僅遺留裸金屬支架平台。故 BP-DES 理論上應能降低晚期支架內血栓帶來的心血管不良事件發生。在先前的綜合薈萃分析已確立 BP-DES 在安全及有效性方面優於 BMS 及第一代 DP-DES。

本篇綜合薈萃分析是目前針對 BP-DES 與第二代 DP-DES 做分析比較最有規模的文章。由本篇分析我們得知 BP-DES 及第二代 DP-DES 支架平台皆有相似的安全及有效性。其中重要的是追蹤超過 1 年發現，BP-DES 在支架血栓的風險相較 DP-DES 並未達到統計有意義的下降 (RR: 0.87, 95% CI: 0.49 to 1.53; p=0.62)。BP-DES 最初是為了克服因耐久性聚合物塗層引發的發炎反應，造成延遲癒合而開發。一些研究顯示需要活性生物吸收的聚合物與耐久性聚合物相比，會產生更多的發炎反應。先前發表的薈萃分析也發現 BP-DES 預後甚至比 DP-DES 還差，或許產生更多的發炎反應能解釋這樣的結論。

本篇綜合薈萃分析，引入更多臨床研究且追蹤時間更長。發現在死亡率 (RR: 1.08, 95% CI: 0.89 to 1.31; p=0.46) 或在支架內血栓 (RR: 0.83, 95% CI: 0.64 to 1.09; p=0.46) 兩組並無顯著差異。除此之外，也觀察到使用 BP-DES 與 DP-DES 相比，支架內血栓事件的數值較低 (0.98% vs. 1.15%)。總而言之，綜整這些數據表明 BP-DES 與 DP-DES 具有類似的安全性和有效性。

本篇綜合薈萃分析另外針對支架厚度，支架材質及 BP-DES 聚合物降解或 DP-DES 藥物釋放時間 (<6 月 or ≥ 6 月) 做次族群分析。顯示以上因子並未顯著影響安全及有效性。

BP-DES 研發的理論基礎就是為了改善支架植入後與血管癒合，以縮短使用雙重抗血小板藥物 (DAPT) 時間。依照不同聚合物降解及藥物釋放動力學，本篇薈萃分析引入的臨床研究，DAPT 使用時間從 3 個月到 12 個月不等。服用至少 6 個月或 12 個月雙重抗血小板藥物，BP-DES 及 DP-DES 支架內血栓的比例相近 (如圖八)。

最近美國心臟學會 (ACC/AHA) 指引，針對穩定冠狀動脈心臟病病患植入 DES 後，建議 DAPT 由 12 個月縮短到 6 個月 (class I)，甚至植入特定 BP-DES 後可以安全地更縮短 DAPT 使用時間。故 BP-DES 在特殊族群病患（如：高出血風險，複雜病灶或服藥順從性差）應用上更有其價值。

這篇文章跟其他綜合薈萃分析類似，都受引入文獻研究設計及品質的限制。另外在探討非常晚期支架內血栓的隨機研究數目及追蹤時間可能也不足。所以還需要更大規模族群及更長時間追蹤的研究。

結論

此綜合薈萃分析顯示生物可降解性聚合物塗層藥物釋放支架 (BP-DES) 在安全性及有效性上皆與第二代耐久性聚合物塗層藥物釋放支架 (DP-DES) 相似。無論標的血管再治療率 (target vessel revascularization, TVR)，心臟相關死亡，心肌梗塞，或支架內血栓二者皆無顯著差異。

TABLE 1 Characteristics of the Included Trials and Stent Used

Study/First Author (Ref. #)	Number of Patients (N)		DAPT Duration (Months)	Follow-Up (Months)	BP-DES Characteristics		
	BP-DES	DP-DES			Stent	Strut Thickness (μm)	Drug
BASKET-PROVE II (20)	765	765	12	24	Nobori	120	Biolimus
BIOFLOW II (21)	298	154	>6	12	Orsiro	60	Sirolimus
BIOSCIENCE (22)	1063	1056	12	24	Orsiro	60	Sirolimus
CENTURY II (23)	551	550	>6	9	Ultimaster	80	Sirolimus
COMPARE II (24)	1,795	912	12	36	Nobori	120	Biolimus
DESSOLVE II (25)	123	61	6 to 12	9	MiStent	64	Sirolimus
EVERBIO II (26)	80	80	>6	9	BioMatrix Flex	112	Biolimus
EVOLVE FHU (27)	193	98	>6	24	Synergy	74	Everolimus
EVOLVE II (28)	846	838	>6	12	Synergy	74	Everolimus
ISAR-TEST 4 (29)	1,299	1,304	>6	60	Yukon choice PC	87	Sirolimus
LONG-DES V (30)	245	255	>12	12	Nobori	120	Biolimus
NEXT (31)	1,617	1,618	>3	36	Nobori	120	Biolimus
Separham et al. (32)	100	100	>12	12	BioMatrix	112	Biolimus
SORT OUT VI (33)	1,497	1,502	>12	12	BioMatrix Flex	112	Biolimus
TARGET I (34)	227	231	>12	12	Firehawk	86	Sirolimus
Xu et al. (35)	168	156	6	24	Tivoli	80	Sirolimus

TABLE 1 Continued

Study/First Author (Ref. #)	BP-DES Characteristics			DP-DES Characteristics			
	Scaffold Material	Drug Release (Months)	Polymer Biodegradation (Months)	Stent	Strut Thickness (μm)	Drug	Scaffold Material
BASKET-PROVE II (20)	SS	6-9	12	Xience Prime	81	Everolimus	Co-Cr
BIOFLOW II (21)	Co-Cr	12	14	Xience Prime	81	Everolimus	Co-Cr
BIOSCIENCE (22)	Co-Cr	12	14	Xience Prime	81	Everolimus	Co-Cr
CENTURY II (23)	Co-Cr	4	4	Xience V	81	Everolimus	Co-Cr
COMPARE II (24)	SS	6-9	12	Xience V/ Prime	81	Everolimus	Co-Cr
DESSOLVE II (25)	Co-Cr	9	3	Endeavor	91	Zotarolimus	Co-Cr
EVERBIO II (26)	SS	6-9	6-9	Promus Element	81	Everolimus	Pl-Cr
EVOLVE FHU (27)	Pl-Cr	3	4	Promus Element	81	Everolimus	Pl-Cr
EVOLVE II (28)	Pl-Cr	3	4	Promus Element	81	Everolimus	Pl-Cr
ISAR-TEST 4 (29)	SS	1	2-3	Xience V	81	Everolimus	Co-Cr
LONG-DES V (30)	SS	6-9	12	Promus Element	81	Everolimus	Pl-Cr
NEXT (31)	SS	6-9	12	Xience/Promus	81	Everolimus	Co-Cr/Pl-Cr
Separham et al. (32)	SS	6-9	12	Xience V	81	Everolimus	Co-Cr
SORT OUT VI (33)	SS	6-9	6-9	Resolute Integrity	91	Zotarolimus	Co-Cr
TARGET I (34)	Co-Cr	1	6-9	Xience V	81	Everolimus	Co-Cr
Xu et al. (35)	Co-Cr	1	6	Endeavor	91	Zotarolimus	Co-Cr

BP-DES = biodegradable polymer drug-eluting stent(s); Co-Cr = cobalt-chromium; DAPT = dual-antiplatelet therapy; DP-DES = durable polymer drug-eluting stent(s); Pl-Cr = platinum-chromium; SS = stainless steel.

▲ 表 1

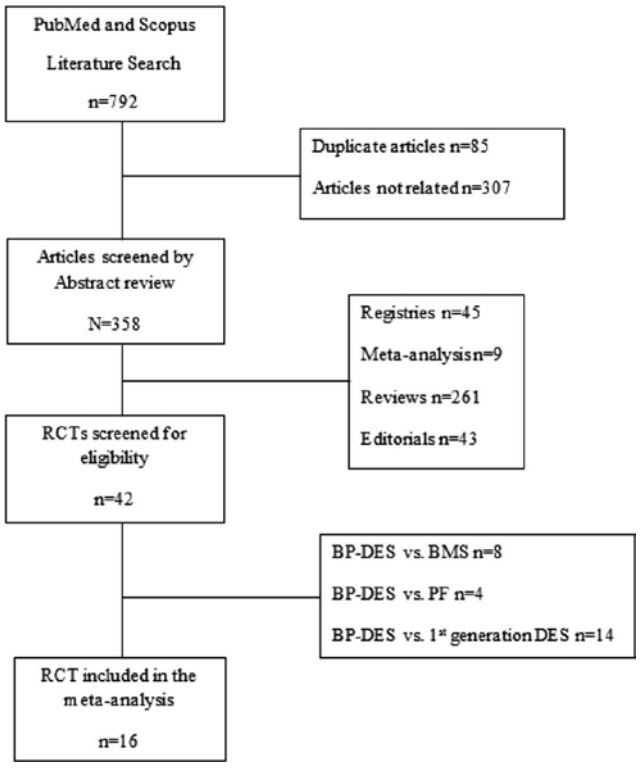
TABLE 2 Cardiac Outcomes

Analysis (No. of Trials Included)	TVR RR (95% CI)	Cardiac Death RR (95% CI)	MI RR (95% CI)	Definite/Probable ST RR (95% CI)
Outcomes at 1 yr (12)	1.08 (0.94-1.23)	1.05 (0.82-1.36)	1.02 (0.87-1.20)	0.82 (0.59-1.12)
Outcomes at the longest follow-up (16)	1.06 (0.96-1.18)	1.08 (0.89-1.31)	1.00 (0.87-1.15)	0.83 (0.64-1.09)
Landmark analysis beyond 1 yr (6)	1.12 (0.93-1.35)	1.13 (0.82-1.56)	0.95 (0.71-1.29)	0.87 (0.49-1.53)
Subgroup analysis				
BP eluting drug				
Biolimus (7)	1.11 (0.97-1.28)	1.18 (0.90-1.54)	1.02 (0.84-1.23)	0.88 (0.56-1.39)
Sirolimus (7)	1.02 (0.86-1.22)	0.99 (0.74-1.32)	0.92 (0.73-1.16)	0.83 (0.59-1.17)
BP-DES strut thickness				
Thin struts (9)	1.00 (0.85-1.17)	0.97 (0.73-1.28)	0.98 (0.81-1.20)	0.81 (0.58-1.13)
Thick struts (7)	1.11 (0.97-1.28)	1.18 (0.90-1.54)	1.02 (0.84-1.23)	0.88 (0.56-1.39)
BP-DES scaffold				
Alloy (8)	0.94 (0.76-1.15)	0.96 (0.65-1.42)	0.95 (0.76-1.20)	0.81 (0.56-1.16)
Stainless steel (8)	1.11 (0.99-1.26)	1.12 (0.89-1.40)	1.03 (0.87-1.22)	0.87 (0.58-1.30)
BP-DES drug release				
<6 months	0.99 (0.81-1.21)	0.96 (0.67-1.38)	1.08 (0.83-1.40)	0.86 (0.47-1.57)
>6 months	1.09 (0.97-1.24)	1.13 (0.89-1.42)	0.97 (0.83-1.14)	0.83 (0.61-1.12)
Polymer degradation				
<6 months	0.99 (0.81-1.21)	0.93 (0.65-1.34)	1.09 (0.84-1.42)	0.84 (0.47-1.51)
>6 months	1.09 (0.97-1.24)	1.14 (0.90-1.43)	0.97 (0.83-1.14)	0.83 (0.61-1.13)
DP eluting drug				
Everolimus (13)	1.09 (0.97-1.21)	1.06 (0.86-1.31)	1.00 (0.87-1.15)	0.86 (0.65-1.14)
Zotarolimus (3)	0.92 (0.68-1.24)	1.18 (0.69-2.03)	1.01 (0.64-1.59)	0.66 (0.29-1.52)
DAPT duration				
≥6 months (8)	0.95 (0.79-1.15)	0.94 (0.66-1.33)	1.09 (0.84-1.42)	0.84 (0.47-1.51)
≥12 months (7)	1.13 (0.99-1.28)	1.14 (0.87-1.50)	0.94 (0.77-1.14)	0.81 (0.59-1.11)

MI = myocardial infarction; RR = risk ratio; ST = stent thrombosis; TVR = target vessel revascularization; other abbreviations as in Table 1.

▲ 表 2

FIGURE 1 PRISMA Diagram



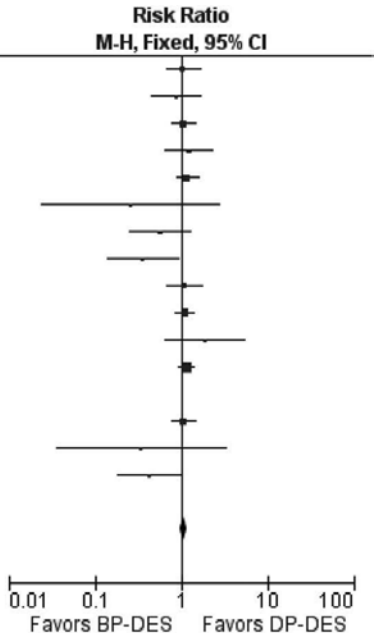
Algorithm of the literature search for studies included in the meta-analysis.
BMS = bare-metal stent(s); BP-DES = biodegradable polymer drug-eluting stent(s); PF = polymer-free; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

▲ 圖 1

FIGURE 2 **Risk Estimates of TVR**

Study or Subgroup	BP-DES Events	BP-DES Total	DP-DES Events	DP-DES Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BASKET-PROVE II	38	765	36	765	5.7%	1.06 [0.68, 1.65]
BIOFLOW-II	22	298	13	154	2.7%	0.87 [0.45, 1.69]
BIOSCIENCE	81	1063	75	1056	11.9%	1.07 [0.79, 1.45]
CENTURY II	21	551	17	550	2.7%	1.23 [0.66, 2.31]
COMPARE II	137	1795	59	912	12.4%	1.18 [0.88, 1.58]
DESSOLVE II	1	117	2	60	0.4%	0.26 [0.02, 2.77]
EVERBIO	8	80	14	80	2.2%	0.57 [0.25, 1.29]
EVOLVE FHU	7	191	10	98	2.1%	0.36 [0.14, 0.91]
EVOLVE II	32	846	29	838	4.6%	1.09 [0.67, 1.79]
ISAR-TEST 4	170	1299	77	652	16.3%	1.11 [0.86, 1.43]
LONG-DES V	9	245	5	255	0.8%	1.87 [0.64, 5.51]
NEXT	177	1617	155	1618	24.6%	1.14 [0.93, 1.40]
SEPARHAM et al	0	100	0	100		Not estimable
SORT OUT VI	71	1497	67	1502	10.6%	1.06 [0.77, 1.47]
TARGET I	1	227	3	231	0.5%	0.34 [0.04, 3.24]
XU et al	7	168	15	156	2.5%	0.43 [0.18, 1.03]
Total (95% CI)		**10859**		**9027**	**100.0%**	**1.06 [0.96, 1.18]**
Total events	782		577			

Heterogeneity: Chi² = 16.56, df = 14 (P = 0.28); I² = 15%
Test for overall effect: Z = 1.17 (P = 0.24)



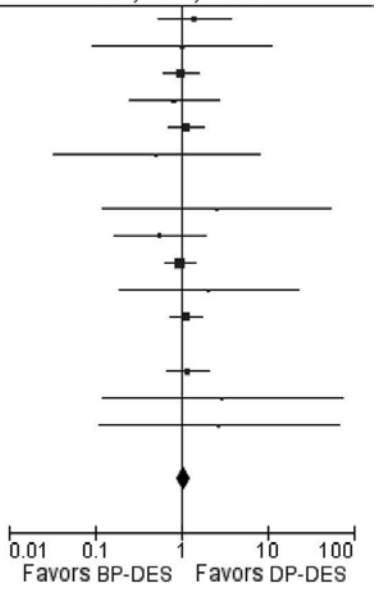
Forest plot reporting the risk ratios (RRs) with 95% confidence interval (CI) of target vessel revascularization in patients treated with BP-DES compared with DP-DES. The **diamond** indicates the point estimate, and the **left and right end of the line** indicate the 95% CI. BP-DES = biodegradable polymer drug-eluting stents; DP-DES = durable polymer drug-eluting stents; M-H = Mantel-Haenszel test; TVR = target vessel revascularization.

▲ 圖 2

FIGURE 3 **Risk Estimates of Cardiac Death**

Study or Subgroup	BP-DES Events	BP-DES Total	DP-DES Events	DP-DES Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BASKET-PROVE II	10	765	7	765	3.6%	1.43 [0.55, 3.73]
BIOFLOW-II	2	298	1	154	0.7%	1.03 [0.09, 11.31]
BIOSCIENCE	33	1063	33	1056	17.2%	0.99 [0.62, 1.60]
CENTURY II	5	551	6	550	3.1%	0.83 [0.26, 2.71]
COMPARE II	52	1795	23	912	15.8%	1.15 [0.71, 1.86]
DESSOLVE II	1	117	1	60	0.7%	0.51 [0.03, 8.06]
EVERBIO	0	80	0	80		Not estimable
EVOLVE FHU	2	191	0	98	0.3%	2.58 [0.12, 53.18]
EVOLVE II	4	846	7	838	3.6%	0.57 [0.17, 1.93]
ISAR-TEST 4	64	1299	33	652	22.8%	0.97 [0.65, 1.47]
LONG-DES V	2	245	1	255	0.5%	2.08 [0.19, 22.81]
NEXT	43	1617	38	1618	19.7%	1.13 [0.74, 1.74]
SEPARHAM et al	0	100	0	100		Not estimable
SORT OUT VI	26	1497	22	1502	11.4%	1.19 [0.68, 2.08]
TARGET I	1	227	0	231	0.3%	3.05 [0.13, 74.54]
XU et al	1	168	0	156	0.3%	2.79 [0.11, 67.91]
Total (95% CI)		**10859**		**9027**	**100.0%**	**1.08 [0.89, 1.31]**
Total events	246		172			

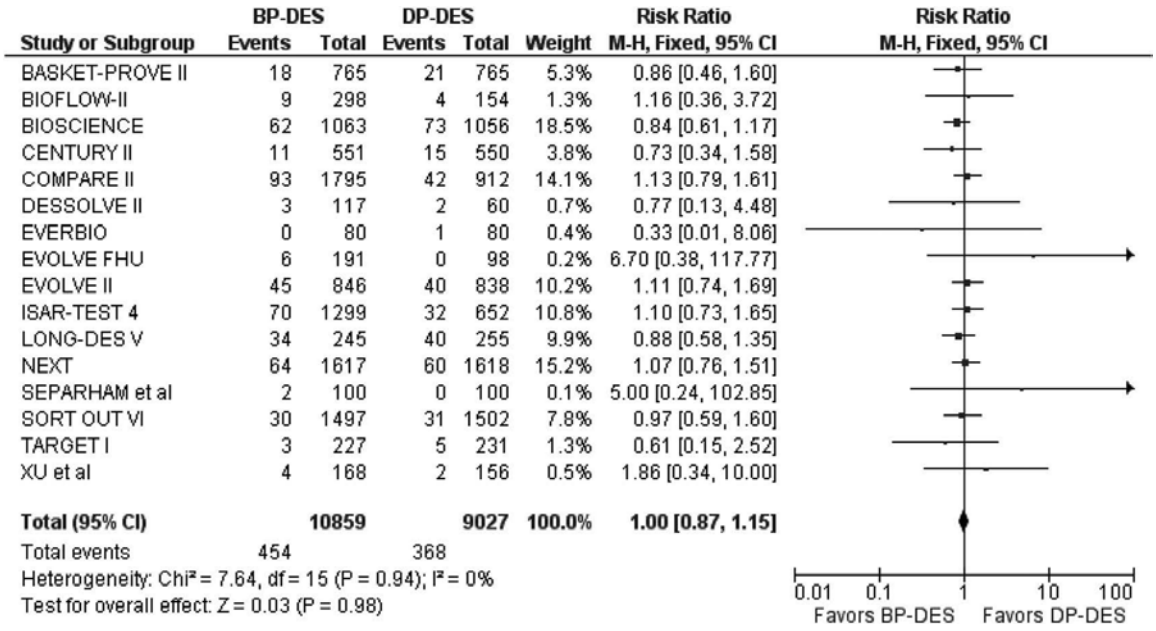
Heterogeneity: Chi² = 3.79, df = 13 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)



Forest plot reporting the RR with 95% CI of the outcome of cardiac death in patients treated with BP-DES compared with DP-DES. The **diamond** indicates the point estimate, and the **left and right end of the line** indicate the 95% CI. Abbreviations as in Figure 2.

▲ 圖 3

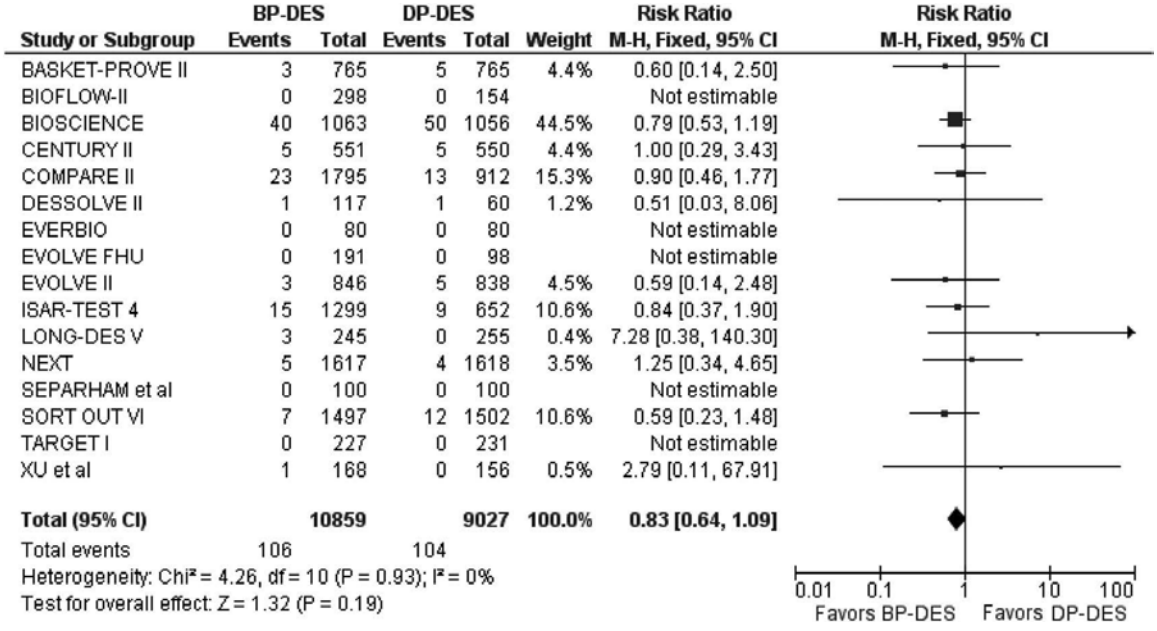
FIGURE 4 Risk Estimates of MI



Forest plot reporting the RR with 95% CI of the outcome of myocardial infarction in patients treated with BP-DES compared with DP-DES. The **diamond** indicates the point estimate, and the **left and right end of the line** indicate the 95% CI. MI = myocardial infarction; other abbreviations as in Figure 2.

▲ 圖 4

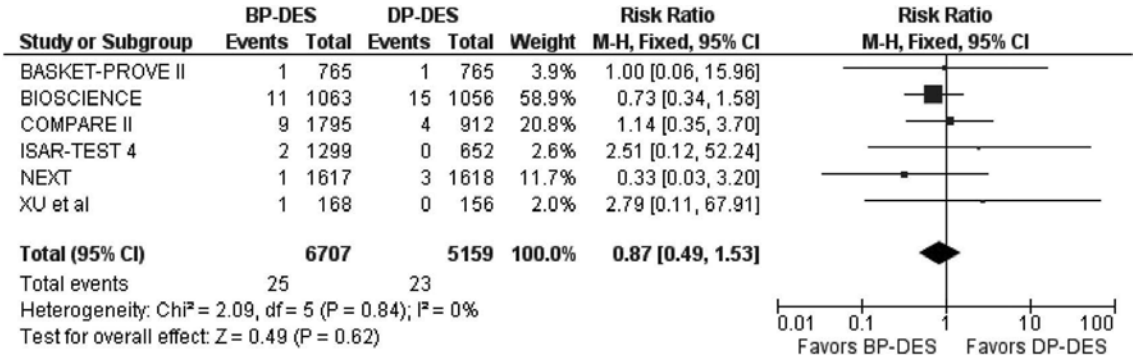
FIGURE 5 Risk Estimates of ST



Forest plot reporting the RR with 95% CI of definite or probable stent thrombosis in patients treated with BP-DES compared with DP-DES. The **diamond** indicates the point estimate, and the **left and right end of the line** indicate the 95% CI. ST = stent thrombosis; other abbreviations as in Figure 2.

▲ 圖 5

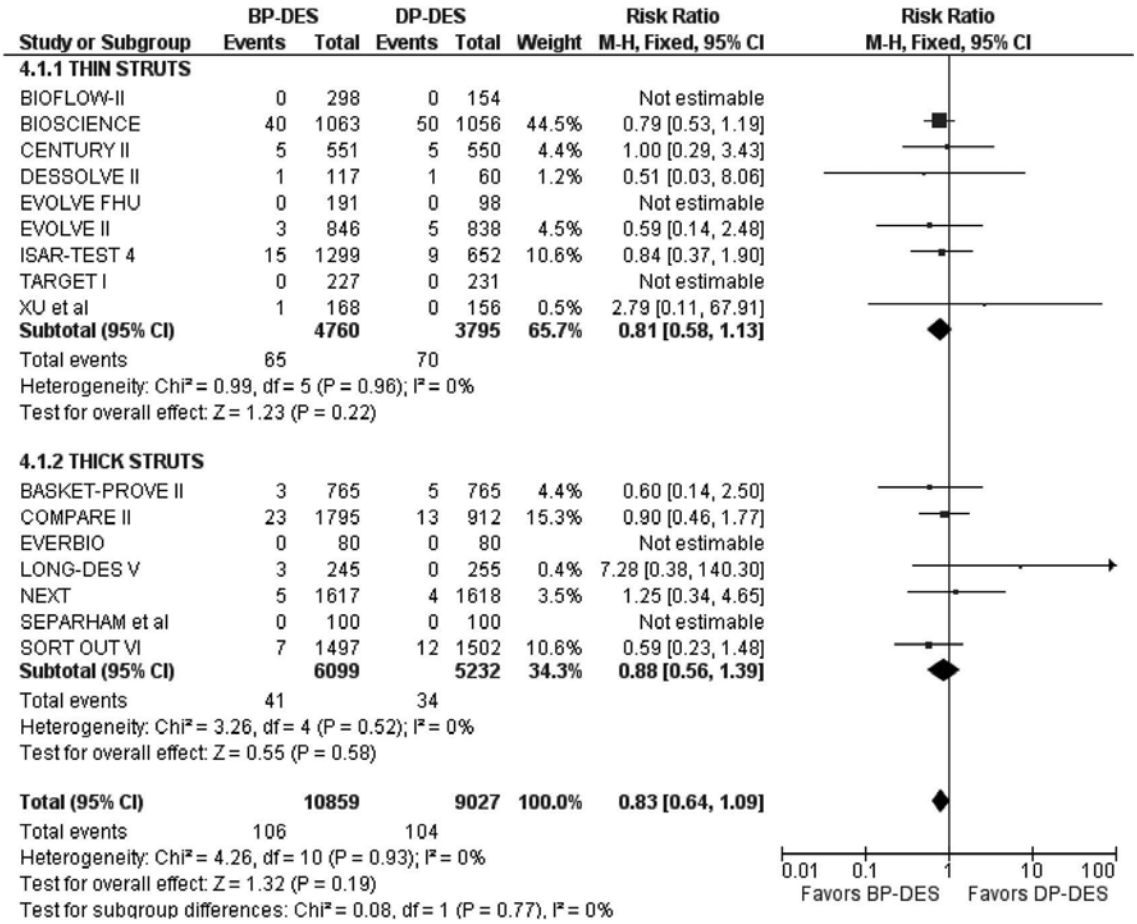
FIGURE 6 Risk Estimates of Very Late ST



Forest plot reporting the RR with 95% CI of very late definite or probable ST beyond 1 year of follow-up in patients treated with BP-DES compared with DP-DES. The **diamond** indicates the point estimate, and the **left and right end of the line** indicate the 95% CI. Abbreviations as in Figures 2 and 5.

▲ 圖 6

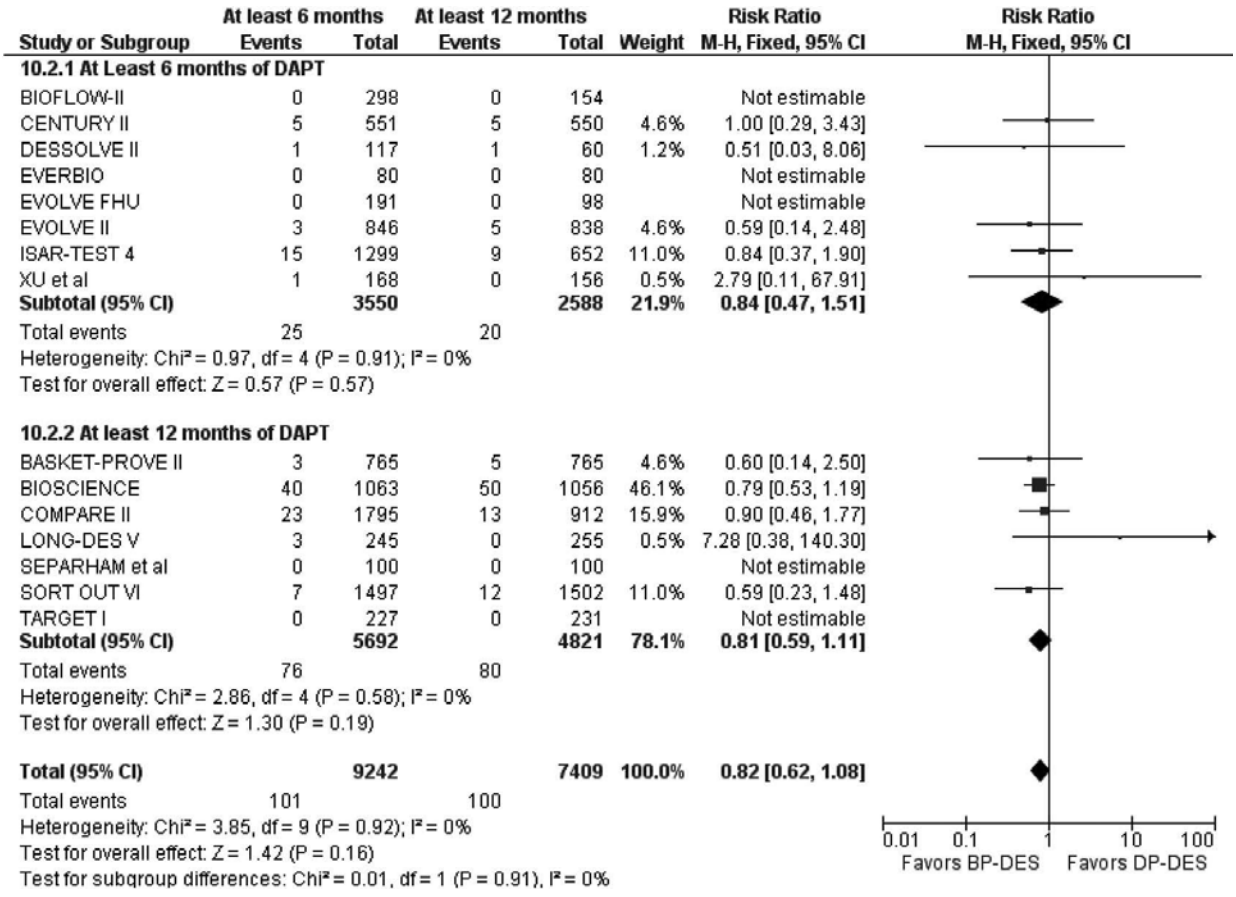
FIGURE 7 Risk Estimates of ST in the Thin- and Thick-Strut BP-DES Subgroups



Subgroup analysis based on the strut thickness of the BP-DES comparing BP-DES to DP-DES for definite or probable ST. The p value in the test for subgroup differences represents the interaction between the subgroups. Abbreviations as in Figures 2 and 5.

▲ 圖 7

FIGURE 8 Risk Estimates of ST in the Subgroups Treated With at Least 6 vs. 12 Months of DAPT



Subgroup analysis based on the duration of dual-antiplatelet therapy (DAPT) comparing BP-DES to DP-DES for definite or probable ST. The p value in the test for subgroup differences represents the interaction between the subgroups. Abbreviations as in Figures 2 and 5.

▲ 圖 8