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CLINICAL RESEARCH
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Clinical impact of direct stenting and interaction with thrombus aspiration in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: Thrombectomy Trialists Collaboration

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Aims Preliminary studies suggest that direct stenting (DS) during percutaneous coronary intervention (PCI) may reduce microvascular obstruction and improve clinical outcome. Thrombus aspiration may facilitate DS. We assessed the impact of DS on clinical outcome and myocardial reperfusion and its interaction with thrombus aspiration among ST-segment elevation myocardial infarction (STEMI) patients undergoing PCI.

Methods and results Patient-level data from the three largest randomized trials on routine manual thrombus aspiration vs. PCI only were merged. A 1:1 propensity matched population was created to compare DS and conventional stenting. Synergy between DS and thrombus aspiration was assessed with interaction *P*-values in the final models. In the unmatched population ($n = 17\,329$), 32% underwent DS and 68% underwent conventional stenting. Direct stenting rates were higher in patients randomized to thrombus aspiration as compared with PCI only (41% vs. 22%; $P < 0.001$). Patients undergoing DS required less contrast (162 mL vs. 172 mL; $P < 0.001$) and had shorter fluoroscopy time (11.1 min vs. 13.3 min; $P < 0.001$). After propensity matching ($n = 10\,944$), no significant differences were seen between DS and conventional stenting with respect to 30-day cardiovascular death [1.7% vs. 1.9%; hazard ratio 0.88, 95% confidence interval (CI) 0.55–1.41; $P = 0.60$; $P_{interaction} = 0.96$) and 30-day stroke or transient ischaemic attack (0.6% vs. 0.4%; odds ratio 1.02; 95% CI 0.14–7.54; $P = 0.99$; $P_{interaction} = 0.81$). One-year results were similar. No significant differences were seen in electrocardiographic and angiographic myocardial reperfusion measures.

Conclusion Direct stenting rates were higher in patients randomized to thrombus aspiration. Clinical outcomes and myocardial reperfusion measures did not differ significantly between DS and conventional stenting and there was no interaction with thrombus aspiration.

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Keywords Myocardial infarction • Myocardial reperfusion • Percutaneous coronary intervention • Thrombectomy • Stents

Introduction

Several strategies have been attempted to improve myocardial reperfusion in patients with ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI). Direct stenting (DS)—stent implantation without balloon pre-dilatation—is thought to do this by reducing distal embolization and thereby microvascular obstruction.[1] The strategy is widely practiced, although no formal guideline recommendations for it exist.[2] Small trials have indeed shown improved myocardial reperfusion and a possible reduction in mortality, but large definitive studies are lacking.[3–7]

Routine use of manual thrombus aspiration in primary PCI resulted in improved myocardial reperfusion and a reduced 1-year cardiac mortality in the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS).[8,9] Patients assigned to thrombus aspiration in TAPAS had substantially higher rates of DS as compared with patients assigned to PCI only. The efficacy of routine thrombus aspiration could not be confirmed in either the much larger Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE)[10] or the Trial of Routine Aspiration Thrombectomy with PCI vs. PCI Alone in Patients with STEMI (TOTAL),[11] prompting international guidelines to advise its use in selected patients only.[2] In the TASTE and TOTAL trials, thrombus aspiration also seemed to facilitate DS, but DS rates were not as high as in TAPAS. It was suggested that a synergistic effect between thrombus aspiration and DS could contribute to explain the differences between TAPAS and the TASTE and TOTAL trials.[12,13] In this study, we used patient-level data from TAPAS, TASTE, and TOTAL to investigate the impact of DS on clinical outcome and myocardial reperfusion and its synergy with thrombus aspiration among patients with STEMI undergoing PCI.

Methods

Study design

As described previously,[14] the Thrombectomy Trialists Collaboration comprises investigators of the three largest randomized clinical trials comparing routine manual thrombus aspiration vs. PCI only in STEMI patients: TAPAS,[8] TASTE,[10] and TOTAL.[11] Individual patient-level data were collaboratively shared, thus accounting for a dataset that included more than 86% of all randomized patients in the field.[12] Data were merged at the Uppsala Clinical Research Center (Uppsala, Sweden) and rigorously reviewed for completeness and consistency. Common data definitions were applied within the collaboration by consensus whenever possible.[14] The three trials complied with the Declaration of Helsinki, each trial was approved by an institutional review board, and participants provided informed consent.

In this study, we used the Thrombectomy Trialists Collaboration data to investigate the impact of DS on myocardial reperfusion and clinical outcome and its synergy with thrombus aspiration. All randomized patients who had undergone PCI for index STEMI were considered. Additional inclusion criteria for this study were implantation of ≥1 stent and non-missing data on DS. Consequently, the final study population differed slightly from our previous report.[14] Direct stenting was defined as implantation of ≥1 stent into the culprit lesion without pre-dilatation. Primary analyses were conducted in the modified intention-to-treat population. For this analysis, patients who had undergone PCI for index STEMI were kept in the study group to which they were originally randomized (i.e. thrombus aspiration or PCI only). A per-protocol (as treated) analysis was conducted as a sensitivity analysis.

Outcomes

Clinical measures of efficacy up to 1-year follow-up were reported in all three trials and included cardiovascular death, all-cause mortality, myocardial infarction, stent thrombosis, and target vessel revascularization. Clinical measures of safety up to 1-year follow-up were available in TASTE and TOTAL only and included stroke or transient ischaemic attack (TIA). Outcome definitions used in each trial are specified in Supplementary material online, *Table S1*. Outcomes in TASTE were obtained from discharge diagnoses in administrative databases and population registries, and were not adjudicated. In this study, the prespecified primary efficacy outcome was 30-day cardiovascular death and the prespecified primary safety outcome was 30-day stroke or TIA.

Data on myocardial reperfusion were available in TAPAS and TOTAL only. Myocardial blush grade was measured directly after PCI, as described previously.[15] Impaired myocardial reperfusion was defined as a myocardial blush Grade of 0 or 1. Electrocardiographic ST-segment resolution was assessed 30–60 min post-PCI, and impaired myocardial reperfusion was defined as ST-segment resolution <70%.[16]

Statistical analysis

Continuous variables were summarized as means ± standard deviations; discrete variables were presented as numbers and percentages. To compare groups, we used Wilcoxon's rank-sum test or Kruskal–Wallis' test for continuous variables and Pearson's χ^2 test for categorical variables. The Kaplan–Meier method was used to display time-to-event data and statistical significance was tested with the log-rank test. To establish the independent impact of DS on clinical outcome and myocardial reperfusion, we first calculated propensity scores to determine the odds of undergoing DS for a given set of baseline and procedural characteristics. Prespecified covariates used to calculate propensity scores were age, sex, hypertension, diabetes, prior myocardial infarction, prior PCI, Killip class IV, culprit vessel (left anterior descending artery vs. other), culprit in proximal vessel, pre-procedural thrombolysis in myocardial infarction (TIMI) flow ≤1, and number of implanted stents. Missing values for each of these covariates were <1%. To avoid loss of data, we used multiple imputation by chained equations to create several datasets over which the estimated propensity scores per patient were averaged. Subsequently, 1:1 propensity matching was performed on propensity score and thrombus aspiration in order to get one conventional stenting control for each DS case. We then computed Cox regression models to calculate hazard ratio's (HRs) and 95% confidence intervals (CIs) for DS for all clinical outcomes adjusting for study. Logistic regression was used to calculate odds ratio's (ORs) for the outcome of stroke or TIA, since the exact time of

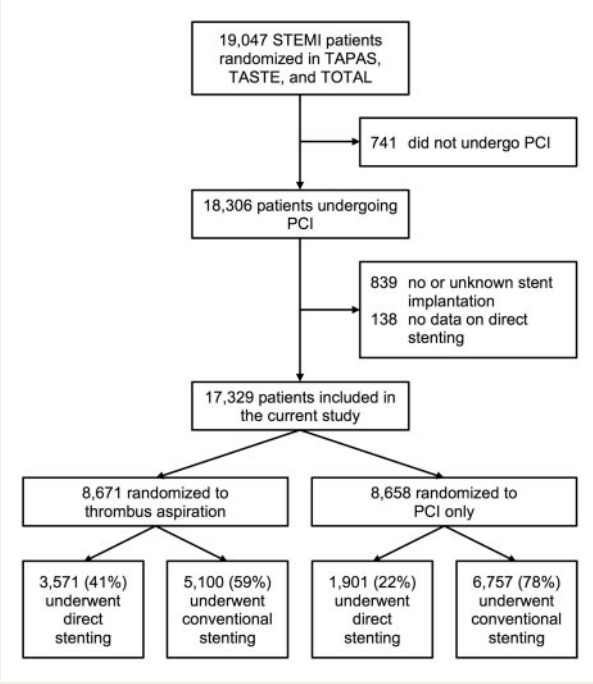


Figure 1 Study flowchart. PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

these events was not documented in the TASTE trial during the initial hospitalization. Logistic regression was also used to establish the impact of DS on myocardial reperfusion measures using the same methodology as described above. Interaction between DS and thrombus aspiration was determined by calculation of the *P*-value for interaction in the final (adjusted) models. Adjusted OR's and HR's for thrombus aspiration were omitted from the outcome tables as they had limited value in a population that was matched based on the propensity of undergoing DS. Sensitivity analyses included a per-protocol analysis (i.e. thrombus aspiration as treated) and a propensity adjusted analysis in the unmatched population. Statistical analyses were performed with R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria) and statistical significance was set at $P < 0.05$ (two-tailed).

Results

A total of 17 329 patients were included; 5472 (32%) underwent DS and 11 857 (68%) underwent conventional stenting (*Figure 1*). Direct stenting rates were almost two-fold higher in patients randomized to thrombus aspiration as compared with PCI only (41% vs. 22%; $P < 0.001$); these percentages were the same in the per-protocol population. Baseline and procedural characteristics are listed in *Table 1*. Patients undergoing DS were slightly younger (61.8 vs. 63.6 years; $P < 0.001$), more likely to smoke (43% vs. 40%; $P < 0.001$), but less likely to have experienced prior myocardial infarction (7.5% vs. 10%; $P < 0.001$) as compared with patients undergoing conventional stenting. No differences were found with respect to infarct related artery, but patients treated with DS had lower rates of pre-procedural TIMI 0/1 flow (70% vs. 77%; $P < 0.001$). While patients undergoing DS had slightly more (1.5 vs. 1.3 stents; $P < 0.001$) and larger (mean diameter 3.2 vs. 3.1 mm; $P < 0.001$) stents implanted, contrast use was lower (162 vs. 172 mL; $P < 0.001$) and fluoroscopy time was shorter (11.1 vs. 13.3 min; $P < 0.001$) as compared with conventional stenting. Notably, patients were more likely to undergo DS in high-volume centres (*Table 1*). Baseline and procedural characteristics by PCI technique in a four-group fashion (DS or conventional stenting and thrombus aspiration or PCI only) are listed in Supplementary material online, *Table S2*.

After 1:1 propensity matching on DS vs. conventional stenting, a population with a total of 10 944 patients was acquired (*Table 1*). This population was used for subsequent analysis. Clinical outcomes in the matched population are listed in *Table 2*. The primary efficacy outcome, 30-day cardiovascular death, occurred in 1.7% of patients treated with DS and 1.9% of patients treated with conventional stenting (HR 0.88, 95% CI 0.55–1.41; $P = 0.60$). No interaction between DS and thrombus aspiration was found ($P_{interaction} = 0.96$), indicating lack of a synergistic effect. Cardiovascular death at 1-year follow-up was 2.7% with DS and 3.0% with conventional stenting (HR 0.89, 95% CI 0.62–1.30; $P = 0.55$; *Figure 2*). There was no interaction with thrombus aspiration ($P_{interaction} > 0.99$).

Thirty-day stroke or TIA, the primary safety outcome, occurred in similar percentages of patients treated with DS and conventional stenting (0.6% vs. 0.4%; OR 1.02, 95% CI 0.14–7.54; $P = 0.99$). No interaction between DS and thrombus aspiration was seen ($P_{interaction} = 0.81$). One-year stroke or TIA results were comparable (*Table 2*). The models in *Table 2* demonstrated that DS as compared with conventional stenting was associated with similar risks of all other clinical outcomes at 30-day and 1-year follow-up including all-cause mortality, myocardial infarction, stent thrombosis, and target vessel revascularization. No interaction with thrombus aspiration was found for any of these outcomes, suggesting lack of synergy between the two procedures.

As a sensitivity analysis, results were recalculated in the per-protocol population where thrombus aspiration was classified according to the treatment received (Supplementary material online, *Table S3*). This yielded similar results, with the exception of a significant association between DS and a lower rate of 1-year target vessel revascularization (4.3% vs. 5.6%; HR 0.73; 95% CI 0.54–0.97; $P = 0.028$). As a further sensitivity analysis, a propensity adjusted (rather than a propensity matched) analysis was conducted in the unmatched population (Supplementary material online, *Table S4*). This yielded similar results as the primary analysis.

Measures of impaired myocardial reperfusion post-PCI are listed in *Table 3*. Direct stenting was not associated with a reduction in incomplete (i.e. <70%) ST-segment resolution (30% vs. 35%; OR 0.84, 95% CI 0.70–1.01; $P = 0.06$) and no interaction with thrombus aspiration was seen ($P_{interaction} = 0.47$). No independent association was found between DS and impaired angiographic myocardial reperfusion either (myocardial blush Grade 0 or 1: 4.7% vs. 5.7%; OR 0.99, 95% CI 0.66–1.47; $P = 0.94$) and there was no interaction with thrombus aspiration ($P_{interaction} = 0.26$).

Principal findings of our study are outlined in the *Take home figure*.

Discussion

We conducted the largest observational study on DS vs. conventional stenting in patients with STEMI undergoing PCI to date. Principal

Table 1 Baseline and procedural characteristics

	Original population			Matched population	
	Direct stenting (*n* = 5472)	Conventional stenting (*n* = 11857)	*P*-value	Direct stenting (*n* = 5472)	Conventional stenting (*n* = 5472)
Baseline					
Age (years)	61.8 ± 12.0	63.6 ± 12.0	<0.001	61.8 ± 12.0	61.7 ± 11.8
Male	4190 (77%)	9084 (77%)	0.95	4190 (77%)	4191 (77%)
Current smoking	2294 (43%)	4639 (40%)	<0.001	2294 (43%)	2354 (44%)
Hypertension	2369 (44%)	5561 (47%)	<0.001	2369 (44%)	2332 (43%)
Diabetes mellitus	806 (15%)	1870 (16%)	0.082	806 (15%)	767 (14%)
Prior myocardial infarction	410 (7.5%)	1185 (10%)	<0.001	410 (7.5%)	360 (6.6%)
Prior PCI	370 (6.8%)	996 (8.4%)	<0.001	370 (6.8%)	332 (6.1%)
Killip Class IV	36 (0.7%)	93 (0.8%)	0.36	36 (0.7%)	33 (0.6%)
Procedural					
Time from symptom onset to PCI			<0.001		
≤6 h	4320 (83%)	8936 (80%)		4320 (83%)	4104 (80%)
6–12 h	704 (14%)	1783 (16%)		704 (14%)	852 (17%)
>12 h	167 (3.2%)	421 (3.8%)		167 (3.2%)	200 (3.9%)
Radial access	3698 (71%)	7474 (66%)	<0.001	3698 (71%)	3476 (67%)
Bivalirudin	2315 (42%)	4960 (42%)	0.56	2315 (42%)	2353 (43%)
Enoxaparin	366 (6.7%)	722 (6.1%)	0.13	366 (6.7%)	327 (6.0%)
Unfractionated intravenous heparin	4683 (86%)	9954 (84%)	0.006	4683 (86%)	4558 (83%)
Glycoprotein IIb/IIIa inhibitor	1669 (31%)	4013 (34%)	<0.001	1669 (31%)	1739 (32%)
Infarct related artery			0.11		
Left anterior descending	2169 (40%)	4858 (41%)		2169 (40%)	2189 (40%)
Circumflex	756 (14%)	1623 (14%)		756 (14%)	725 (13%)
Right	2510 (46%)	5269 (45%)		2510 (46%)	2513 (46%)
Left main	7 (0.1%)	33 (0.3%)		7 (0.1%)	9 (0.2%)
Graft	24 (0.4%)	44 (0.4%)		24 (0.4%)	22 (0.4%)
Proximal vessel	3444 (63%)	7191 (61%)	0.004	3444 (63%)	3424 (63%)
Preprocedural TIMI 0/1 flow	3779 (70%)	9119 (77%)	<0.001	3779 (70%)	3755 (69%)
TIMI thrombus grade			<0.001		
0, No thrombus present	430 (7.9%)	991 (8.4%)		430 (7.9%)	520 (9.5%)
1, Possible thrombus present	621 (11%)	1391 (12%)		621 (11%)	700 (13%)
2, Definite thrombus present <0.5 vessel diameter	322 (5.9%)	641 (5.4%)		322 (5.9%)	319 (5.9%)
3, Definite thrombus present 0.5–2.0 vessel diameters	1013 (19%)	1740 (15%)		1013 (19%)	860 (16%)
4, Definite thrombus present >2.0 vessel diameters	1156 (21%)	1985 (17%)		1156 (21%)	927 (17%)
5, Total occlusion	1912 (35%)	5052 (43%)		1912 (35%)	2121 (39%)
Thrombus aspiration—randomized	3571 (65%)	5100 (43%)	<0.001	3571 (65%)	3435 (63%)
Thrombus aspiration—as treated	3588 (66%)	5211 (44%)	<0.001	3588 (66%)	3452 (63%)
≥1 Drug-eluting stent	2457 (45%)	5636 (48%)	0.001	2457 (45%)	2678 (49%)
Number of stents	1.5 ± 0.8	1.3 ± 0.7	<0.001	1.5 ± 0.8	1.4 ± 0.7
Stent length (mm)	28.4 ± 16.2	27.9 ± 15.1	0.50	28.4 ± 16.2	30.0 ± 16.8
Stent diameter (mm)	3.2 ± 0.5	3.1 ± 0.5	<0.001	3.2 ± 0.5	3.1 ± 0.5
Contrast volume (mL)[a]	162 ± 103	172 ± 96	<0.001	162 ± 103	175 ± 105
Fluoroscopy time (min)	11.1 ± 21	13.3 ± 23	<0.001	11.1 ± 21	13.7 ± 22
Site PCI volume			<0.001		
Tertile 1	1637 (30%)	3989 (34%)		1637 (30%)	1923 (35%)
Tertile 2	1989 (36%)	4550 (39%)		1989 (36%)	1963 (36%)
Tertile 3	1844 (34%)	3271 (28%)		1844 (34%)	1564 (29%)

PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
[a]TASTE and TOTAL only.

Table 2 Clinical outcome in the matched population[a]

	Direct stenting ($n = 5472$), n (%)	Conventional stenting ($n = 5472$), n (%)	P-value	aHR (95% CI)	P-value	Thrombus aspiration ($n = 7006$), n (%)	PCI only ($n = 3938$), n (%)	$P_{interaction}$
30-day cardiovascular death	93 (1.7)	104 (1.9)	0.43	0.88 (0.55–1.41)	0.60	122 (1.7)	75 (1.9)	0.96
1-year cardiovascular death	148 (2.7)	165 (3.0)	0.32	0.89 (0.62–1.30)	0.55	197 (2.8)	116 (3.0)	>0.99
30-day stroke or TIA[b]	31 (0.6)	20 (0.4)	0.16	1.02 (0.14–7.54)	0.99	38 (0.6)	13 (0.3)	0.81
1-year stroke or TIA[b]	64 (1.2)	49 (0.9)	0.19	1.02 (0.29–3.62)	0.98	77 (1.2)	36 (0.9)	0.95
30-day all-cause mortality	98 (1.8)	109 (2.0)	0.44	0.89 (0.56–1.40)	0.60	128 (1.8)	79 (2.0)	0.96
1-year all-cause mortality	183 (3.4)	199 (3.7)	0.40	0.99 (0.70–1.39)	0.94	245 (3.5)	137 (3.5)	0.58
30-day myocardial infarction	52 (1.0)	65 (1.2)	0.22	0.78 (0.43–1.43)	0.42	72 (1.0)	45 (1.2)	0.90
1-year myocardial infarction	122 (2.3)	143 (2.7)	0.18	0.87 (0.58–1.30)	0.47	165 (2.4)	100 (2.6)	0.92
30-day stent thrombosis	39 (0.7)	51 (0.9)	0.20	0.66 (0.35–1.25)	0.20	48 (0.7)	42 (1.1)	0.49
1-year stent thrombosis	59 (1.1)	72 (1.3)	0.25	0.69 (0.40–1.19)	0.18	73 (1.1)	58 (1.5)	0.36
30-day TVR	81 (1.5)	124 (2.3)	0.002	0.67 (0.43–1.05)	0.08	119 (1.7)	86 (2.2)	0.90
1-year TVR	227 (4.3)	297 (5.6)	0.002	0.77 (0.58–1.03)	0.07	319 (4.7)	205 (5.3)	0.92

aHR, adjusted hazard ratio; CI, confidence interval; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; TVR, target vessel revascularization.
[a]Note that thrombus aspiration vs. PCI only is a randomized comparison while direct vs. conventional stenting is not.
[b]TASTE and TOTAL only; reported as odds ratio.

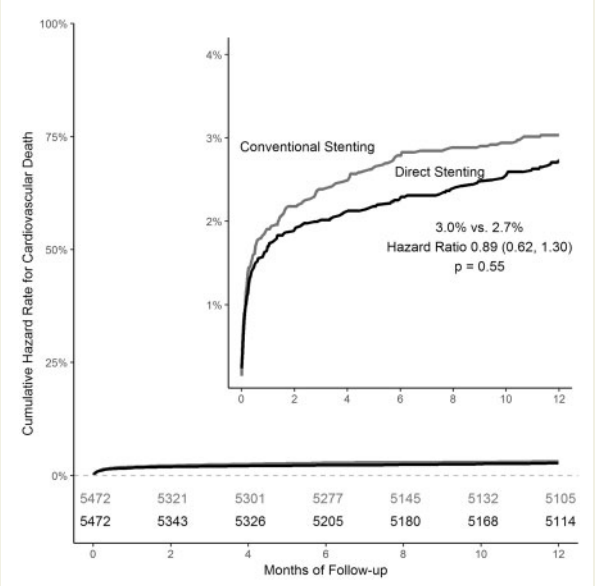


Figure 2 Occurrence of cardiovascular death up to 1 year in the propensity matched population.

findings of our study are: (i) thrombus aspiration may facilitate DS as was suggested by the substantially higher rate of patients undergoing DS after randomization to thrombus aspiration as compared with PCI only; (ii) patients treated with DS required less contrast and had shorter fluoroscopy times, while the number of implanted stents was slightly higher; (iii) DS was not significantly associated with improved 30-day and 1-year clinical outcome as compared with conventional stenting; (iv) no interaction between DS and thrombus aspiration was found for any of the measures of clinical outcome, suggesting absence of a synergistic effect when the two procedures are combined; (v) DS was not associated with improved myocardial reperfusion.

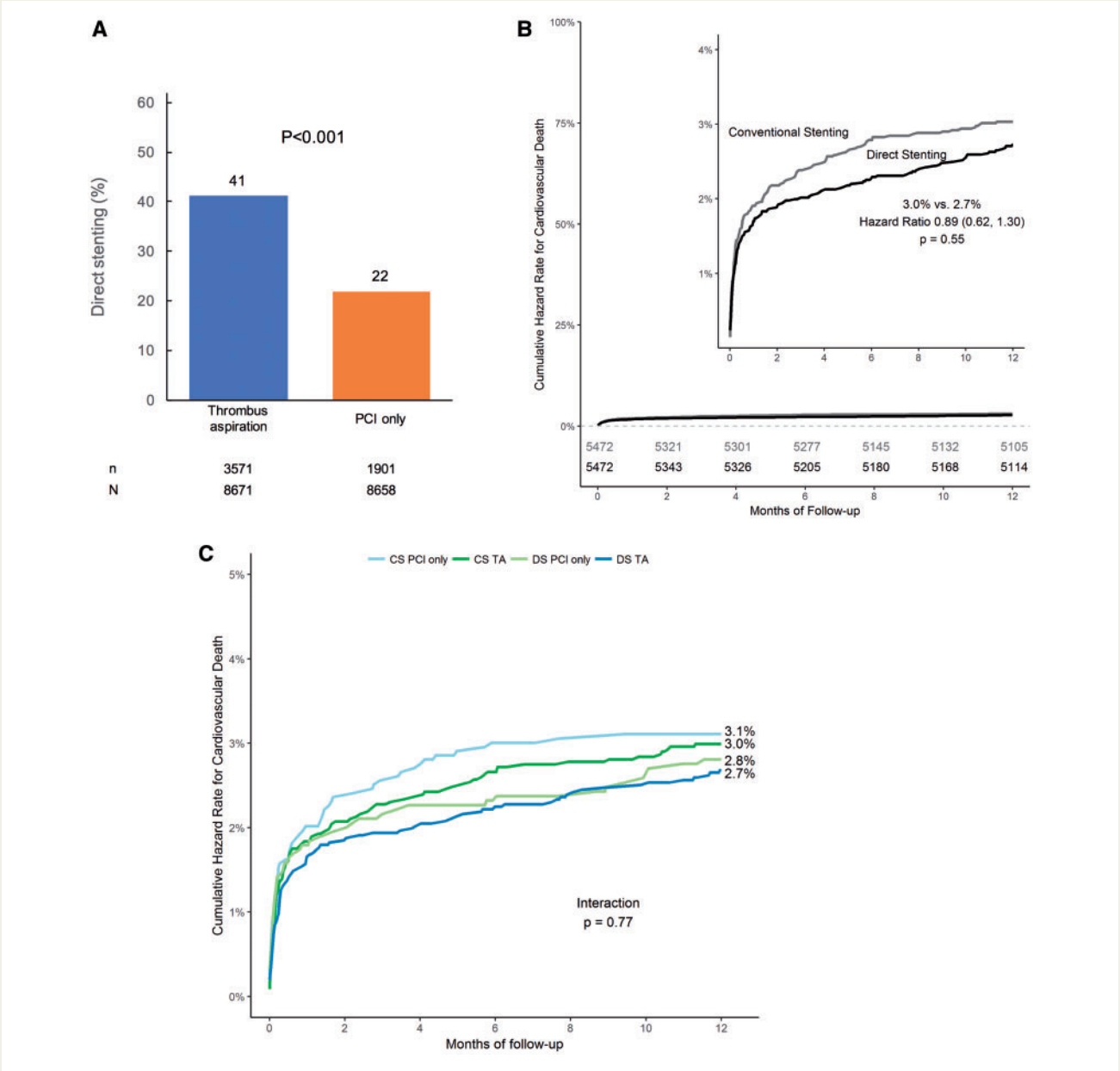
Several potential advantages of DS over conventional stenting are possible.[1] It has been postulated that omission of pre-dilatation in DS might reduce the risk of thrombus fragmentation and distal embolization with subsequent microvascular obstruction and impaired myocardial reperfusion, vessel wall injury might be reduced, and some dissections might be sealed the moment they are created. Furthermore, DS may reduce radiation exposure, radiographic contrast use, and procedural duration and costs. Potential disadvantages of DS include failure to reach or cross the lesion, lesion/stent mismatch due to suboptimal lesion visualization, and underexpansion of the stent in calcified lesions.[1] We did indeed find reductions in contrast use and fluoroscopy time with DS. Clinical outcome and myocardial reperfusion were not significantly better with DS as compared with conventional stenting, although it should be noted that a moderate benefit from DS on clinical outcome could not be ruled out given the effect estimates and wide confidence intervals we found in our study. We found no evidence of harm associated with DS. Particularly, rates of stent thrombosis and target vessel revascularization up to 1 year were similar in DS and conventional stenting, which is a reassuring signal in the light of concerns of lesion/stent mismatch with DS. In the per-protocol analysis (thrombus aspiration as treated), DS was even associated with a reduction in 1-year target vessel revascularization. However, this result warrants cautious interpretation as it was only seen in one sensitivity analysis. A contemporary randomized trial is warranted to definitively address the efficacy and safety of this common procedure. Such a trial would require a large sample size, but this is feasible if a simple trial design is chosen.

DS has been studied in five small clinical trials randomizing a total of 754 patients.[3–7] A recent meta-analysis of these trials reported on a higher rate of ST-segment resolution (69% vs. 60%; $P = 0.05$) and a

Table 3 **Impaired myocardial reperfusion post-percutaneous coronary intervention in the matched population[a]**

	Direct stenting ($n = 3241$), *n* (%)	Conventional stenting ($n = 3293$), *n* (%)	*P*-value	aOR (95% CI)	*P*-value	Thrombus aspiration ($n = 4262$), *n* (%)	PCI only ($n = 2272$), *n* (%)	$P_{interaction}$
ST-segment resolution <70%	972 (30)	1152 (35)	<0.001	0.84 (0.70–1.01)	0.06	1365 (32)	759 (33)	0.47
Myocardial blush grade 0 or 1	153 (4.7)	189 (5.7)	0.07	0.99 (0.66–1.47)	0.94	223 (5.2)	119 (5.2)	0.26

aOR, adjusted odds ratio; CI, confidence interval; PCI, percutaneous coronary intervention.
[a]TAPAS and TOTAL only; note that thrombus aspiration vs. PCI only is a randomized comparison while direct vs. conventional stenting is not.



Take home figure (*A*) Direct stenting rates were almost two-fold higher in patients randomized to thrombus aspiration as compared with percutaneous coronary intervention only, suggesting that thrombus aspiration may facilitate direct stenting. (*B*) One-year cardiovascular death and other clinical outcomes did not differ significantly after direct stenting or conventional stenting in the propensity matched population. (*C*) No interaction was found between direct stenting and thrombus aspiration for any of the clinical outcomes, suggesting lack of synergy when the two procedures are combined. DS, direct stenting; PCI, percutaneous coronary intervention; TA, thrombus aspiration.

reduction in in-hospital mortality (0.3% vs. 2.1%; $P = 0.02$) with DS as compared with conventional stenting.[17] Reductions in procedural time and contrast volume were also reported. However, it is important to note the limitations of these trials. They were all conducted in the late '90s through early '00s and thus contained several obsolete treatment elements including antiplatelet therapy with ticlopidine and implantation of bare-metal stents. Moreover, inclusion was limited to STEMI patients in only one trial,[6] while the other trials included a broader spectrum of patients with acute coronary syndromes,[4,5,7] and, in one trial, even some patients with stable angina.[3]

More contemporary observational studies have also been published, reporting on reductions in fluoroscopy time[18] and contrast use[13,18] as well as improved myocardial reperfusion,[19] and reductions in 1-year all-cause mortality with DS.[13,18,19] The positive results of these studies in the light of our neutral results could be due to chance, but possible alternative explanations are as follows. First, two of these studies were conducted in an all-comers registry and thus included a broader spectrum of STEMI patients than our current trial population.[13,19] It is conceivable that these studies included more high-risk patients with complex and calcified lesions who have a poor clinical outcome and are unlikely to be treated with DS, resulting in a bias toward superiority of DS despite multivariable adjustment. Second, these studies were moderately sized (1419 through 2528 patients), yielding less than 20 actual events per study in the DS group for all-cause mortality at 1-year follow-up. It is well known that limited power reduces the reliability of multivariable models and increases the chance of spurious findings. By conducting a study that is larger than all prior studies in the field combined, we had reasonable event counts for common (e.g. all-cause mortality) and less common (e.g. stent thrombosis) clinical events. Third, the field may be affected by publication bias, as some neutral studies may not find their way to publication. Nonetheless, a single centre experience that reported on lack of a mortality reduction with DS was recently published.[20]

The combination of thrombus aspiration and DS comprises two potentially beneficial elements. The first element is facilitation of DS by thrombus aspiration. Thrombus aspiration has the potential to remove the thrombotic component of a culprit lesion allowing for better visualization of lesion length and reference vessel diameter of the underlying stenosis, thus enhancing the number of lesions amenable for DS. Indeed, our study supports the hypothesis that thrombus aspiration facilitates DS as was evidenced by an almost two-fold higher DS rate after thrombus aspiration as compared with PCI only. This finding is also in line with previous observational studies.[13,18,19] The second element pertains to actual synergy between thrombus aspiration and DS, which means that the combination of these two procedures that are both thought to improve myocardial reperfusion results in a benefit that is greater than the sum of the two separate interventions. We did not find evidence of such synergy in our study. Our analysis suggests that differences in DS rates cannot sufficiently explain differences in clinical outcomes between TAPAS and the TASTE and TOTAL trials. It is important to note that definitive evidence of synergy can only be derived from a large randomized clinical trial using a 2×2 factorial design and such a trial has not been conducted to date. Nonetheless, it is worth to mention the PIHRATE trial in this context.[21] This small trial randomizing 196 STEMI patients to thrombus aspiration with DS vs. PCI only with pre-dilatation was negative on its primary endpoint (60 min post-procedural ST-segment resolution >70, 54% vs. 45%; $P = 0.29$).

Limitations

Several limitations of our study should be noted. First, this article is a *post hoc* analysis of trial data. While patients were randomized to thrombus aspiration vs. PCI only, performance of DS was at the operator's discretion. Accordingly, our analysis is susceptible to bias. Although, we rigorously adjusted for confounders, we cannot exclude the possibility of residual confounding by unmeasured factors. Specifically, it has been reported that patients with calcified lesions exhibit poorer myocardial reperfusion.[22] Since these patients are less likely to undergo DS, this could be a source of residual confounding in favour of DS. Second, it is important to note that outcomes reported for thrombus aspiration vs. PCI only are different as compared with the dedicated meta-analysis, we previously published on this topic.[14] Differences are due to unavoidable exclusion of additional patients as we outlined in *Figure 1* and due to the matching procedure. Consequently, event rates reported in this subpopulation cannot be used to draw conclusions on the efficacy or safety of thrombus aspiration. Third, not all data were available in all the participating trials. Data on myocardial reperfusion were unavailable in TASTE and TAPAS did not document the occurrence of stroke or TIA. Fourth, outcomes were not adjudicated in TASTE, a registry-based randomized trial.

Conclusions

Patients randomized to thrombus aspiration were more likely to undergo DS. It required less contrast and had shorter fluoroscopy time. Clinical outcomes and myocardial reperfusion measures with DS and conventional stenting did not differ significantly and there was no interaction with thrombus aspiration. A large randomized trial is warranted to definitively address the efficacy and safety of this common procedure.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: During the conduct of the TOTAL trial, S.S.J. received an institutional research grant from Medtronic. During the conduct of the TASTE trial, S.J. received institutional research grants from Medtronic, Vascular Solutions, and Terumo Inc. Since then, he has received institutional research grants from Boston Scientific, Abbot Vascular, AstraZeneca, and The Medicines Company. He has received honoraria from AstraZeneca, The Medicines Company, Bayer, and Boston Scientific. The other authors report no conflicts. The authors declare that all of the manuscript's content is original.

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