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Vascular Complications Associated With Arteriotomy Closure Devices in Patients Undergoing Percutaneous Coronary Procedures

A Meta-Analysis

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OBJECTIVES This study was designed to assess the safety of arteriotomy closure devices (ACDs) versus mechanical compression by meta-analysis in patients undergoing percutaneous transfemoral coronary procedures.

BACKGROUND Although ACDs are widely applied for hemostasis after percutaneous endovascular procedures, their safety is controversial.

METHODS Randomized, case-control, and cohort studies comparing access-related complications using ACDs versus mechanical compression were analyzed. The primary end point was the cumulative incidence of vascular complications, including pseudoaneurysm, arteriovenous fistula, retroperitoneal hematoma, femoral artery thrombosis, surgical vascular repair, access site infection, and blood transfusion.

RESULTS A total of 30 studies involving 37,066 patients were identified. No difference in complication incidence between Angio-Seal and mechanical compression was revealed in the diagnostic (Dx) setting (odds ratio [OR] 1.08, 95% confidence interval [CI] 0.11 to 10.0) or percutaneous coronary interventions (PCI) (OR 0.86, 95% CI 0.65 to 1.12). Meta-analysis of randomized trials only showed a trend toward less complications using Angio-Seal in a PCI setting (OR 0.46, 95% CI 0.20 to 1.04; $p = 0.062$). No differences were observed regarding Perclose in either Dx (OR 1.51, 95% CI 0.24 to 9.47) or PCI (OR 1.21, 95% CI 0.94 to 1.54) setting. An increased risk in complication rates using VasoSeal in the PCI setting (OR 2.25, 95% CI 1.07 to 4.71) was found. The overall analysis favored mechanical compression over ACD (OR 1.34, 95% CI 1.01 to 1.79).

CONCLUSIONS In the setting of Dx angiography, the risk of access-site-related complications was similar for ACD compared with mechanical compression. In the setting of PCI, the rate of complications appeared higher with VasoSeal. (J Am Coll Cardiol 2004;44:1200–9) © 2004 by the American College of Cardiology Foundation

Arteriotomy closure devices (ACD) have emerged as an alternative to traditional mechanical compression after percutaneous coronary intervention (PCI) (1–2). These devices have the potential to reduce the time to hemostasis, facilitate patient mobilization, decrease hospital length of stay, and improve patient satisfaction (3–13). However, the issue of ACD safety with respect to vascular complications remains controversial (14). To provide an overall assessment of vascular complications, we performed a meta-analysis of published studies that evaluated the use of various ACD versus mechanical compression in patients undergoing coronary procedures with the transfemoral approach.

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METHODS

Literature search and study selection. The methodology of this meta-analysis was performed following the recommendations of the Cochrane Collaboration and Meta-analyses of Observational Studies in Epidemiology (MOOSE) group (15,16). To identify eligible manuscripts, a database search (Cochrane Library, MEDLINE, CINAHL, EMBASE) for literature published since 1991 was performed in April 2003 using the following keywords: "closure device," "hemostasis," "femoral," "arterial," "vascular access," "suture," "collagen," "angiography," "angioplasty," and "heart catheterization." In addition, the reference lists of the identified articles were critically reviewed.

Literature search and assessment of relevance of each source were performed by two independent reviewers (E.N., A.H.). Disagreements about whether a trial should be included were resolved by discussion and adjudicated by a third reviewer (G.D.). Studies considered for the meta-

Abbreviations and Acronyms

ACD = arteriotomy closure devices
CI = confidence interval
Dx = diagnostic
OR = odds ratio
PCI = percutaneous coronary intervention
RCT = randomized controlled trial

analysis included randomized control trials, cohort, and case-control studies that met all of the following criteria: 1) were published as full articles; 2) had well-described protocols of intervention, including a precise report on each of the major vascular complications; and 3) compared access-related complications using ACD versus mechanical compression (manual, by means of hand compression, sandbag, C-clamp, or Femostop) in patients undergoing PCI with transfemoral access.

Pooled average rate of complications plus patients' main demographics and procedural data were extracted from each manuscript. The primary outcome measure was cumulative incidence of major vascular complications, including pseudoaneurysm requiring ultrasound-guided compression or surgical repair; arteriovenous fistula; retroperitoneal hematoma causing hemodynamic compromise, surgery, blood transfusion, prolonged hospitalization and/or death; femoral artery thrombosis (vessel occlusion requiring surgery or thrombolysis); surgical vascular repair; access-site infection necessitating treatment with antibiotics and/or surgical drainage; and blood transfusion.

Studies assessing Angio-Seal (Angio-Seal Daig, Minnetonka, Minnesota) (3,6,9,11,12,17–23), VasoSeal (VasoSeal Datascope Inc., Montvale, New Jersey) (4,5,19,24–30), and Perclose (ProStar Plus or TecStar; Perclose, Redwood City, California) (7,8,10,12,13,18,19,21,23,29,31–35) were included in the meta-analysis. Data on various devices as well as on diagnostic (Dx) catheterization and PCI were assessed separately and in combination. In addition, a separate meta-analysis for randomized trials only was performed. Studies using different ACD sheath sizes were also analyzed.

Statistical analysis. All statistical analyses were performed using the software "Comprehensive Meta-Analysis" (Biostat Inc., Englewood, New Jersey). Study effects are presented using odds ratios (OR). An odds ratio <1 indicates a better outcome for ACD, whereas an OR >1 indicates a better outcome for mechanical compression. The OR and 95% confidence intervals (CI) for combined studies were calculated using Mantel-Haenszel fixed-effects models unless evidence of between-study heterogeneity existed, in which case Mantel-Haenszel random effects models were used (36). The random effects model allows some of the variation in ORs between studies to reflect true underlying differences and leads to a wider CI (36). Heterogeneity across studies in the meta-analysis was assessed using the Q statistic (15).

RESULTS

A total of 81 potentially eligible studies were identified. Of these, 51 were excluded (Appendix) for one or more of the following reasons: the lack of a control arm (n = 31), ACD use in a setting other than percutaneous coronary procedure (n = 3), the lack of precise report on each of the major vascular complications (n = 8), combined analysis of vascular complications in ACD group that included >1 device (n = 3), bias in patient selection (n = 3), review article (n = 3), use of historical control (n = 2), and repeat data reporting (n = 2).

The remaining 30 studies meeting the inclusion criteria and the important demographic and procedural determinants of patient outcome are summarized in Tables 1 and 2. The number of enrolled patients in the studies ranged from 60 to 10,001 (8,34), with 57% of studies having ≥100 patients in each arm. In all studies, most patients were men (range 56% to 94%) (5,8). The proportion of patients with diabetes ranged from 8% to 43% (4,8). The majority of studies (73%) used a ≥8-F device sheath. There were no significant baseline differences among ACD patients and control groups in each of the included studies.

The selected studies included a total of 37,066 patients (12,596 and 24,470 patients in the device and control groups, respectively). Among the included publications, there were 18 randomized studies (2,339 and 2,197 patients) (3–11,13,24–28,31–33) and 12 nonrandomized studies (10,257 and 22,273 patients) (12,17–23,29,30,34,35). In 12 studies, the ACD compared with mechanical compression was Angio-Seal (3,6,9,11,12,17–23); in 9 studies, VasoSeal (5,6,25–30); and in 15 studies, Perclose (7,8,10,12,13,18,19,21,23,31–35). Six studies compared more than one device versus conventional compression techniques (12,18,19,21,23,29). Separate data on Dx and PCI procedures were provided in 6 (6,7,12,25,30,34) and 19 (4,6–13,17,18,20–23,25–29,32–35) studies, respectively, whereas 6 other studies presented mixed data on Dx and PCI procedures without clearly distinguishing between Dx and PCI settings (3,5,19,22,24,31).

Angio-Seal versus mechanical compression. Among 12 studies that evaluated Angio-Seal versus mechanical compression, 2 were conducted in the Dx setting, 8 in the setting of PCI, and 4 presented results in a mixed setting (both Dx and PCI) (Fig. 1). Individual study sample sizes varied from 150 to 6,262 patients (11,20). Two studies had small sample sizes (<100 patients in each arm) (11,23). Studies analyzing the use of Angio-Seal versus mechanical compression in either the Dx or PCI setting were statistically homogeneous (Fig. 1). However, significant heterogeneity in complication rates was present in studies that analyzed mixed Dx and PCI procedures, as well as all studies. Meta-analysis did not reveal a benefit for either technique in the setting of Dx (OR 0.71, 95% CI 0.22 to 2.24), PCI (OR 0.86, 95% CI 0.65 to 1.12), or mixed procedures (OR 2.04, 95% CI 0.64 to 6.45), as well as in the

Table 1. Study and Patient Characteristics

Study (Ref.)	Year	Procedure Type	Patients		Age, Mean ± SD (yrs)		Male (%)		Diabetics (%)		Clinical Follow-Up
			ACD	Control	ACD	Control	ACD	Control	ACD	Control	
Angio-Seal											
Kussmaul et al. (3)*	1995	Dx+PCI	218	217	61 ± 11	62 ± NA	72.9	71.9	16.1	18.0	8 weeks
Ward et al. (6)*	1998	Dx, PCI†	202	102	61.7 ± 12	64.7 ± 10	69.3	70.6	24.3	25.5	14–30 days
Amin et al. (11)*	2000	PCI	75	75	58 ± NA	59.5 ± NA	77.3	78.7	21.3	20.0	In-hospital
Chevalier et al. (9)*	2003	PCI	306	306	≥70: 32%	≥70: 35%	NA	NA	17.0	19.0	7 days
Cremonesi et al. (17)	1998	PCI	411	387	59 ± 15	55 ± 18	77.5	76.9	20.7	25.1	In-hospital
Eidt et al. (22)	1999	Dx+PCI	425	1,662	51.7 ± NA	NA	60.0	NA	NA	NA	In-hospital
Cura et al. (18)	2000	PCI	411	2,099	63.1 ± 11	63.5 ± 11	76.9	69.0	25.1	30.5	In-hospital
Carey et al. (19)	2001	Dx+PCI	742	1,019	62 ± NA	63 ± NA	60.0	61.0	NA	NA	In-hospital
Dangas et al. (20)	2001	PCI	373	5,889	64 ± 11	64 ± 12	68.1	68.0	26.0	29.0	In-hospital
Duffin et al. (12)	2001	Dx, PCI†	537	469	63 ± 13	63 ± 13	70	65	17.0	19.0	30 days
Applegate et al. (21)	2002	PCI	524	1,824	62 ± 12	64 ± 12	55.9	63.0	25.0	20.0	In-hospital
Assali et al. (23)	2003	PCI	39	123	60 ± 13.7	62.7 ± 11.8	64.1	65.9	30.8	35.0	In-hospital
All Angio-Seal studies			4,263	14,172							
VasoSeal											
Schrader et al. (24)*	1992	Dx+PCI	50	50	58.5 ± 10.2	58.5 ± 9.2	86.0	90.0	NA	NA	6 weeks
Sanborn et al. (25)*	1993	Dx, PCI†	246	209	60.6 ± NA	62.0 ± NA	73.6	67.5	17.9	16.7	30 days
Camenzind et al. (26)*	1994	PCI	62	62	59 ± 12	60 ± 11	80.6	85.5	NA	NA	In-hospital
Slaughter et al. (4)*	1995	PCI	51	50	57.0 ± 10.5	57.7 ± 9.3	82	74	8	14	28–35 days
Von Hoch et al. (27)*	1995	PCI	154	155	63 ± NA	60 ± NA	81.2	76.1	NA	NA	3–7 days
Gwechenberger et al. (5)*	1997	Dx+PCI	33	29	59.8 ± 8.1	56.9 ± 10.8	93.9	82.8	NA	NA	7 days
Silber et al. (28)*	1999	PCI	74	76	59.8 ± 9.0	58 ± 9.2	78.0	76.0	25.0	19.0	In-hospital
Chamberlin et al. (29)	1999	PCI	52	77	61.8 ± NA	63.7 ± NA	67.3	72.7	NA	NA	In-hospital
Schickel et al. (30)	1999	Dx	81	95	58.1 ± NA	52.8 ± NA	63.0	52.6	NA	NA	3 days
Carey et al. (19)	2001	Dx+PCI	937	1,019	61 ± NA	63 ± NA	60.0	61.0	NA	NA	In-hospital
All VasoSeal studies			1,740	1,822							
Perclose											
Gerckens et al. (7)*	1999	Dx, PCI†	298	292	60 ± 9	62 ± 8	69.1	70.9	11.0	13.0	In-hospital
Baim et al. (31)*	2000	Dx+PCI	251	264	61.5 ± 11.7	62.9 ± 12.3	76.1	67.0	21.9	22.0	30 days
Carere et al. (32)*	2000	PCI	50	50	62 ± 11	59 ± 12	78.0	78.0	NA	NA	3 days
Noguchi et al. (8)*	2000	PCI	30	30	63 ± 10	61 ± 12	90.0	83.3	43.3	40.0	In-hospital
Wetter et al. (33)*	2000	PCI	50	50	58.8 ± 10.5	59.9 ± 9.7	NA	NA	NA	NA	In-hospital
Rickli et al. (13)*	2002	PCI	96	97	62 ± 11	59 ± 10	74.0	83.5	NA	NA	In-hospital
Nasu et al. (10)*	2003	PCI	93	83	65 ± 10	64 ± 9	69.9	81.9	NA	NA	In-hospital
Cura et al. (18)	2000	PCI	408	2,099	63.6 ± 11	63.5 ± 11	72.1	69.0	24.5	30.5	In-hospital
Chamberlin et al. (29)	1999	PCI	56	77	62.9 ± NA	63.7 ± NA	71.4	72.7	NA	NA	In-hospital
Carey et al. (19)	2001	Dx+PCI	1,001	1,019	62 ± NA	63 ± NA	57.0	61.0	NA	NA	In-hospital
Duffin et al. (12)	2001	Dx, PCI†	492	469	62 ± 12	63 ± 13	70.0	71.0	17.1	19.0	30 days
Applegate et al. (21)	2002	PCI	2,177	1,824	62 ± 12	64 ± 12	71.0	63.0	25.0	20.0	In-hospital
Kahn et al. (34)	2002	Dx, PCI†	1,420	8,581	66.2 ± 8	66.4 ± 8	66.7	66.6	17.2	16.3	In-hospital
Kornowski et al. (35)	2002	PCI	48	48	64 ± 13	63 ± 13	70.8	64.6	20.8	22.9	In-hospital
Assali et al. (23)	2003	PCI	123	123	59.6 ± 11.1	62.7 ± 11.8	69.1	65.9	30.9	35.0	In-hospital
All Perclose studies			6,593	15,106							

*Randomized studies. †Both separate and combined analysis is provided for diagnostic procedures and percutaneous coronary interventions.
ACD = arteriotomy closure device; Dx = diagnostic; NA = not available; PCI = percutaneous coronary interventions.

Table 2. Device and Procedural Characteristics

Study (Ref.)	Device Failure (%)	Sheath Size (F) in ACD	Sheath Size (F) in Control	Dx Procedures (%)		Mean ACT ± SD (s)		GP IIb/IIIa Use (%)	
				ACD	Control	ACD	Control	ACD	Control
Angio-Seal studies									
Kussmaul et al. (3)	4.0	8	<8F: 59.6% 8F: 40.4%	74.8	70.0	176 ± 69	156 ± 53	0	0
Cremonesi et al. (17)	4.1	8	<8F: 45.6% 8F: 54.4%	0	0	355 ± 43	178 ± 26	3.2	0
Ward et al. (6)	4.0	8	<8F: 97% 8F: 3%	100.0	100.0	158.5 ± 58	144.0 ± 42	NA	NA
Eidt et al. (22)	8.0	8	NA	NA	NA	NA	NA	NA	NA
Amin et al. (11)	4.0	8	8F: 100%	0	0	NA	NA	0	0
Cura et al. (18)	1.5	Mean 7.8F ± 0.5	Mean 7.8F ± 0.5	0	0	264 ± NA	280 ± NA	56.0	58.0
Carey et al. (19)	NA	NA	NA	29.0	30.0	NA	NA	42.0	1.0
Dangas et al. (20)	NA	8	NA	0	0	277 ± 59	268 ± 54	6.2	5.5
Duffin et al. (12)	4.5	8	<8F: 70% 8F: 30%	72.1	42.0	290 ± 94	292 ± 126	13.6	29.0
Applegate et al. (21)	2.9	≥8F: 92%	<8F: 5% ≥8F: 95%	0	0	277 ± NA	268 ± NA	100.0	100.0
Assali et al. (23)	15.4	8	<8F: 91.1% 8F: 8.9%	0	0	261 ± 50	254 ± 51	100.0	100.0
Chevalier et al. (9)	3.2	8	<8F: 92% ≥8F: 8.0%	0	0	247 ± 43	130 ± 24	2.0	1.0
VasoSeal studies									
Schrader et al. (24)	0	11.5	<8F: 60% 8F: 40%	60	60	NA	NA	0	0
Sanborn et al. (25)	NA	11.5	<8F: 29.2% ≥8F: 70.8%	36.6	35.9	NA	NA	0	0
Camenzind et al. (26)	6.0	11.5	<8F: 82% ≥8F: 8%	0	0	NA	NA	0	0
Slaughter et al. (4)	20.0	8	8F: 100%	0	0	381 ± 152	151 ± 71	0	0
Von Hoch et al. (27)	0.0	11.5	8F: 100%	0	0	NA	NA	0	0
Gwechenberger et al. (5)	0.0	11.5	NA	45.5	44.8	NA	NA	NA	NA
Chamberlin et al. (29)	21.2	NA	NA	0	0	172.7 ± NA	157.2 ± NA	100.0	100.0
Schickel et al. (30)	NA	NA	NA	100.0	100.0	NA	NA	0	0
Silber et al. (28)	NA	11.5	NA	0	0	PTT reported	PTT reported	NA	NA
Carey et al. (19)	NA	NA	NA	15.0	30.0	NA	NA	29.0	1.0
Perclose studies									
Chamberlin et al. (29)	14.3	NA	NA	0	0	241 ± NA	157.2 ± NA	100.0	100.0
Gerckens et al. (7)	5.7	6F: 68.2% 8F: 31.8%	5.5F to 8F	68.1	67.8	NA	NA	NA	NA
Baim et al. (31)	8.8	8F and 10F	<8F: 42% ≥8F: 58.0%	55.8	54.5	NA	NA	8.0	12.9
Carere et al. (32)	10.0	8	8F: 100%	0	0	350 ± 92	157 ± 64	0	0
Cura et al. (18)	1.5	Mean 7.8F ± 0.5	Mean 7.8F ± 0.5	0	0	264 ± NA	280 ± NA	65.0	58.0
Noguchi et al. (8)	3.4	8	8F: 100%	0	0	288 ± 49	151 ± 27	NA	NA
Wetter et al. (33)	8.0	6F: 33% 7F: 67%	6F: 48% 7F: 52%	0	0	290 ± 83.6	277.4 ± 67.2	0	0
Carey et al. (19)	NA	NA	NA	29.0	30.0	NA	NA	60.0	1.0
Duffin et al. (12)	8.9	6F or 8F	<8F: 43% ≥8F: 57%	0	0	316 ± 103	292 ± 126	35.8	50.0
Applegate et al. (21)	2.9	≥8F-97%	<8F: 5% ≥8F: 95%	0	0	277 ± NA	268 ± NA	100.0	100.0
Kahn et al. (34)	6.8	8	<8F: 93.2% ≥8F: 6.8%	0	0	205 ± 26	202 ± 24	100.0	100.0
Kornowski et al. (35)	6.2	6	6F: 100%	0	0	247 ± 68	262 ± 87	58.3	43.8
Rickli et al. (13)	NA	6F: 39 pts 7P: 57 pts	6F: 55.7% 7F: 44.3%	0	0	286 ± 92	275 ± 62	0	0
Assali et al. (23)	8.1	NA	<8F: 91.1% 8F: 8.9%	0	0	250 ± 61	261 ± 50	100.0	100.0
Nasu et al. (10)	NA	8F or 10F	7F to 8F: 95% 9F to 10F: 5%	0	0	NA	NA	0	0

ACD = arteriotomy closure device; Dx = diagnostic; GP = glycoprotein; NA = not available; PCI = percutaneous coronary interventions; PTT = partial thromboplastin time; SD = standard deviation.

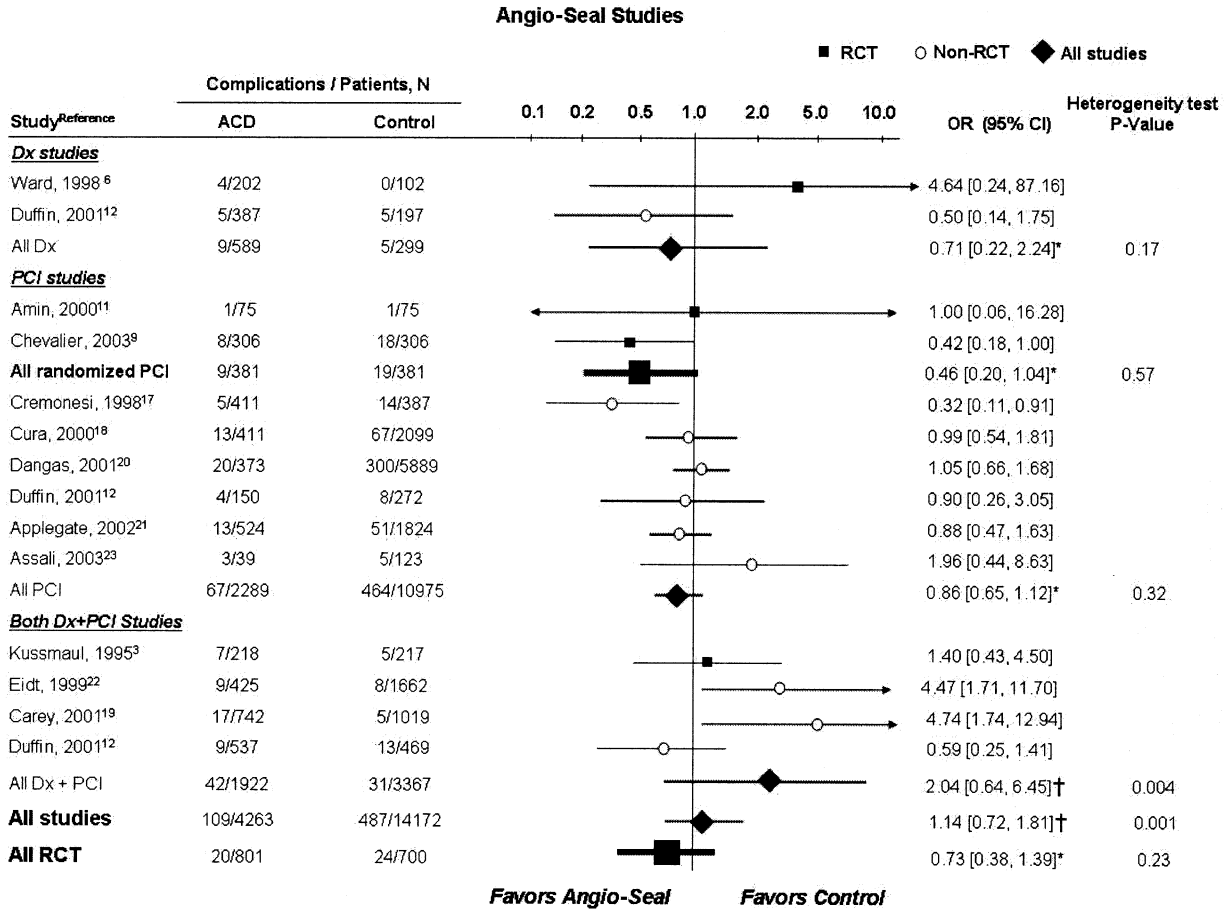

Figure 1. Odds ratio (OR) and 95% confidence interval (CI) of vascular access-related complication rate in patients with Angio-Seal and mechanical compression (control) in diagnostic (Dx), percutaneous coronary intervention (PCI), mixed (Dx+PCI), or any setting. RCT = randomized controlled trials. *Fixed effects model; †random effects model.

overall assessment (OR 1.14, 95% CI 0.72 to 1.81). Meta-analysis of randomized trials only showed a trend toward less complications using Angio-Seal in a PCI setting (OR 0.46, 95% CI 0.20 to 1.04; p = 0.062). The results of randomized studies in any setting were similar to the results of all studies included in this analysis.

VasoSeal versus mechanical compression. Among 10 studies that evaluated VasoSeal versus mechanical compression, 2 were conducted in the Dx setting, 6 in the setting of PCI, and 4 in the mixed setting (Fig. 2). Individual study sample sizes varied from 62 to 1,956 patients (5,19). The majority of studies (8 of 10) had small sample sizes. There was no statistical evidence of heterogeneity across the studies (Fig. 2). In the setting of Dx procedures, there was no significant risk in complication rates in the ACD group compared with mechanical compression (OR 1.85, 95% CI 0.15 to 22.39); however, 2 identified studies included too small a number of patients to draw conclusions. There was no significant difference in the incidence of vascular complications when studies on mixed Dx and PCI procedures were analyzed together (OR 1.86, 95% CI 0.85 to 4.06). However, meta-analysis favored conventional technique in the setting of PCI (OR 2.52, 95% CI 1.36 to 4.65) and in any setting (OR 2.27, 95% CI 1.35 to 3.80). The results of meta-analysis of randomized trials only in the setting of PCI and in any setting were close to the results of meta-analysis of all studies.

Perclose versus mechanical compression. Fifteen studies evaluated Perclose versus mechanical compression: 3 in the Dx setting, 13 in the setting of PCI, and 5 in the mixed setting (Fig. 3). Individual study sample sizes varied from 60 to 10,001 patients (8,34). Eight studies were small, representing 53.3% of all Perclose studies. Statistical evidence of heterogeneity for the complication rate was present in studies assessing Dx and mixed procedures as well as in all studies, but not in studies related to PCI (Fig. 3). No difference in the risk of complications was found in studies assessing ACD versus mechanical compression in either setting (OR 1.51, 95% CI 0.24 to 9.47 for Dx; OR 1.21, 95% CI 0.94 to 1.54 for PCI; and OR 1.37, 95% CI 0.88 to 2.14 for any setting).

Again, the results of meta-analysis of randomized trials assessed only in the setting of PCI, mixed setting, or any setting were similar to the results of meta-analysis of all studies.

Any device versus mechanical compression. When all studied devices were analyzed versus mechanical compression, statistical evidence of heterogeneity was present

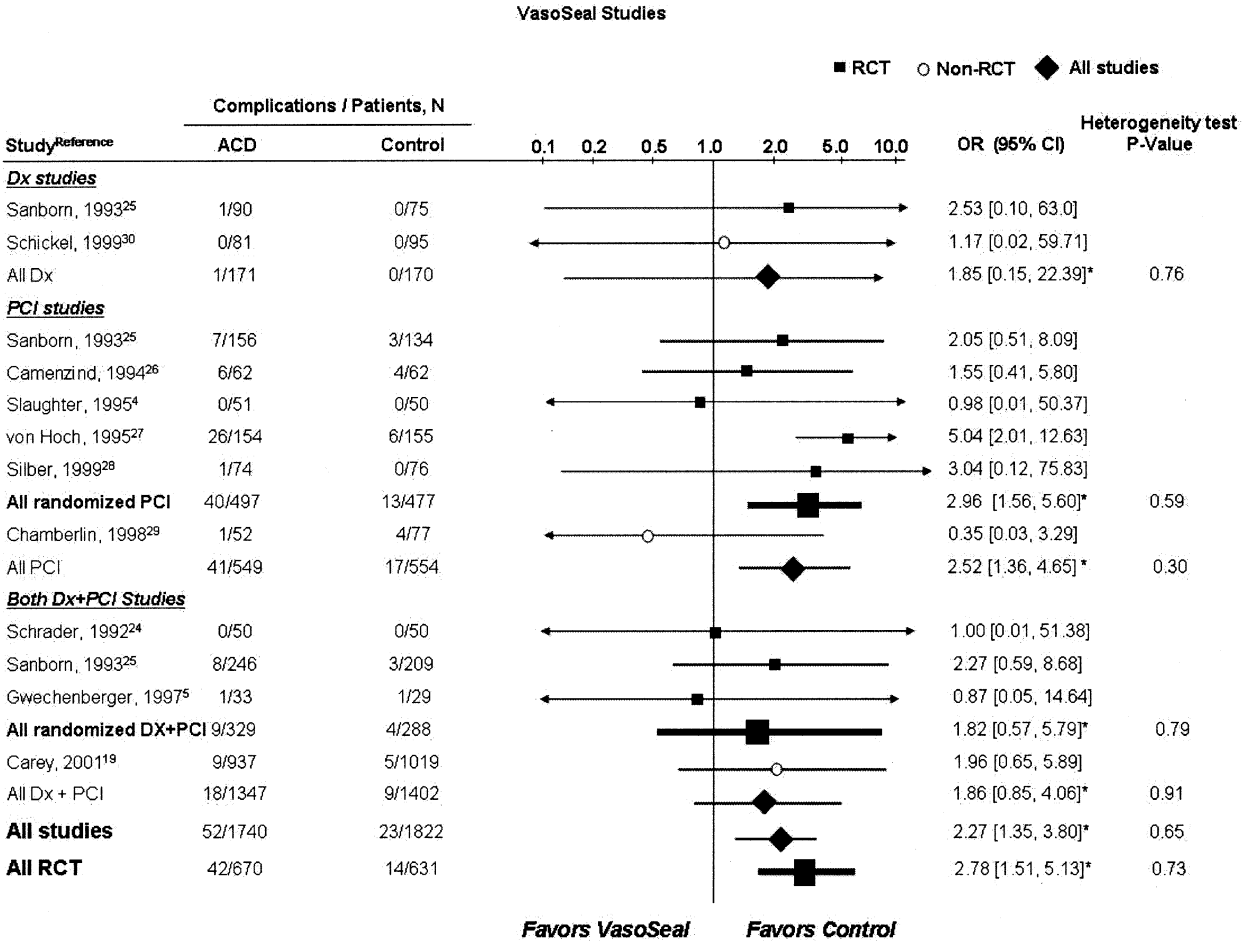

Figure 2. Odds ratio (OR) and 95% confidence interval (CI) of vascular access-related complication rate in patients with VasoSeal and mechanical compression (control) in diagnostic (Dx), percutaneous coronary intervention (PCI), mixed, or any setting. *Fixed effects model. RCT = randomized controlled trials.

across studies related to 1) Dx procedures, 2) mixed Dx and PCI procedures, and 3) any procedure. There was no significant heterogeneity across randomized trials only in either setting. There was no significant difference in the risk of complications using either technique in the randomized trials. The same was also found in the meta-analysis of all studies in the Dx and PCI settings. Meta-analysis of all included studies in mixed Dx and PCI setting and all settings together favored conventional technique over ACD (Fig. 4).

Percutaneous coronary interventions using glycoprotein IIb/IIIa inhibitors. Major vascular complication rates using Angio-Seal or Perclose versus mechanical compression in patients treated with glycoprotein IIb/IIIa inhibitors were compared in three and four studies, respectively (8,21,23,29,34). There was no evidence of significant heterogeneity across these studies ($p = 0.30$ and 0.76, respectively). The use of either Angio-Seal or Perclose was associated with similar complication rates to mechanical compression (OR 1.17, 95% CI 0.87 to 1.58; and OR 1.05, 95% CI 0.77 to 1.44, respectively).

Percutaneous coronary interventions using different device sheath size. Of nine studies applying Perclose in the PCI setting, four studies used closure device with sheath size 6- or 7-F (7,13,33,35) whereas the device sheath size was ≥8 French in the other five studies (8,10,21,32,34). There was no evidence of heterogeneity between studies included in either group ($p = 0.95$ and 0.91, respectively). The use of Perclose was associated with the same risk of complications as traditional compression regardless of device sheath size (OR 0.76, 95% CI 0.27 to 2.19 for the smaller sheath; OR 1.12, 95% CI 0.81 to 1.54 for the larger sheath).

DISCUSSION

The present meta-analysis found no significant risk with respect to vascular complications between ACD and mechanical compression in the setting of diagnostic procedures; the same was applicable for the PCI setting, with the exception of the VasoSeal device, which appeared to have a disadvantage compared to mechanical compression.

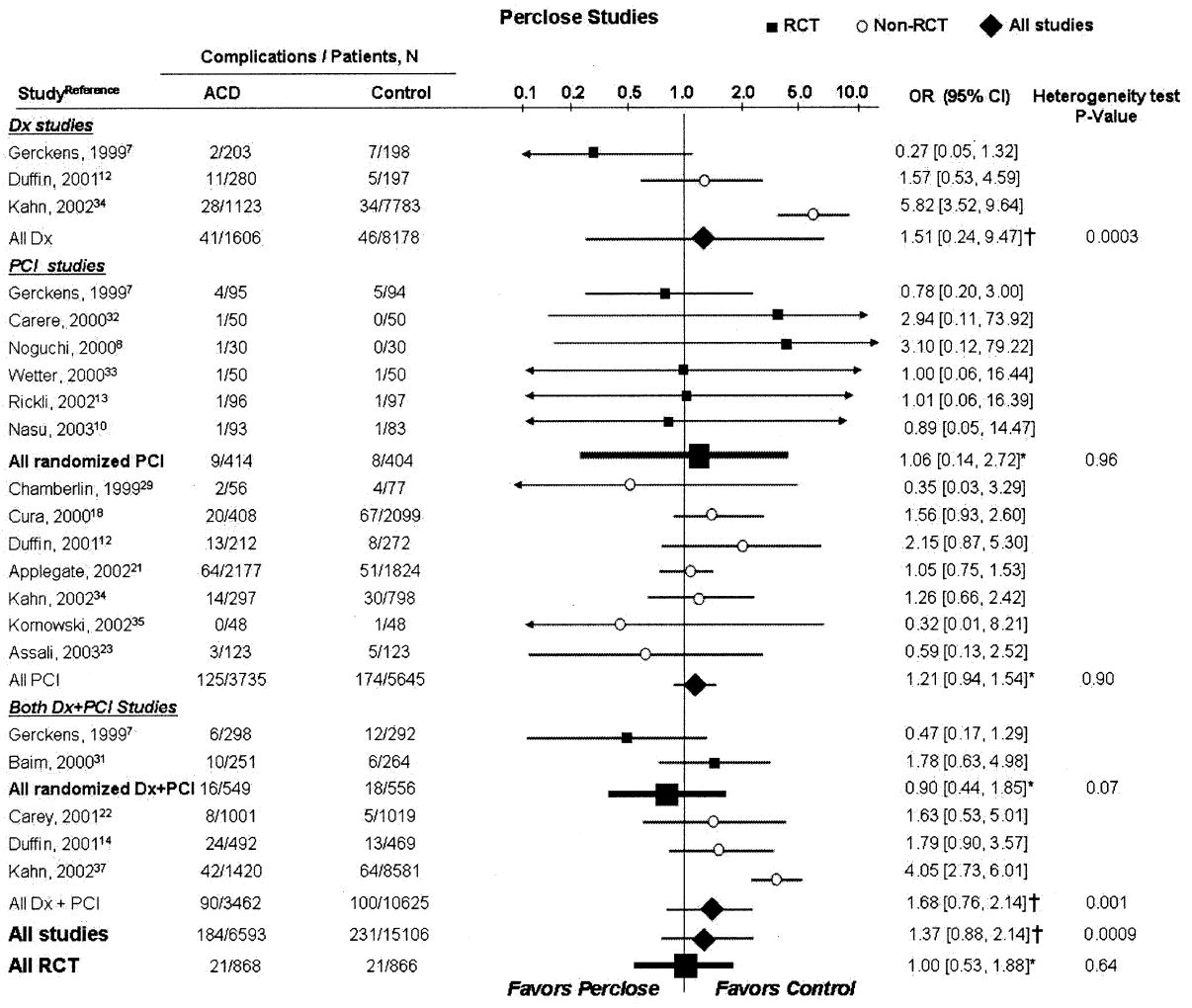

Figure 3. Odds ratio (OR) and 95% confidence interval (CI) of vascular access-related complication rate in patients with Perclose and mechanical compression (control) in diagnostic (Dx), percutaneous coronary intervention (PCI), mixed, or any setting. *Fixed effects model; †random effects model. RCT = randomized controlled trials.

Methodologic aspects of this meta-analysis. The following important issues regarding our approach to this meta-analysis should be addressed. Primarily, our meta-analysis included both randomized and observational trials because the current literature lacks large-scale randomized control trials with sample size sufficient to reveal superiority or noninferiority of ACD compared with mechanical compression. In fact, the proportion of patients from randomized trials in the current analysis was rather low: only 8% in Angio-Seal and Perclose studies, 36% in the VasoSeal studies, and 10% in all studies.

The application of meta-analysis to observational studies has been advocated when large randomized trials are not available (16). However, there are potentially more bias sources in these studies relative to randomized trials. This may make an estimation of a single outcome potentially misleading. Inclusion of small (even randomized) studies into a meta-analysis might limit power to detect difference in major complications because of relatively low incidence of this outcome measure. This was especially true in the analysis of VasoSeal: 8 of 10 studies on this device had <100 patients in each arm. In addition, the issue of publication bias may threaten the validity of any meta-analysis, especially for observational studies. Failure to include unpublished trials introduces bias toward overestimating the effectiveness of an intervention (in this case, ACD).

Given the differences of patients that may be included in randomized controlled trials (RCT) and other studies, we also performed a meta-analysis of RCT only on this subject. The results in the setting of PCI were similar to the overall results. However, given the paucity of trials in the setting of diagnostic procedures, it was not possible to perform a meta-analysis separately for RCT in this setting.

The issue of heterogeneity. Several baseline characteristics of included patients and study design details differed among the analyzed trials. These discrepancies may have contributed to the heterogeneous results. The sources of heterogeneity in ACD studies are various and are related to patient (age, gender, body mass index, the presence of diabetes, and

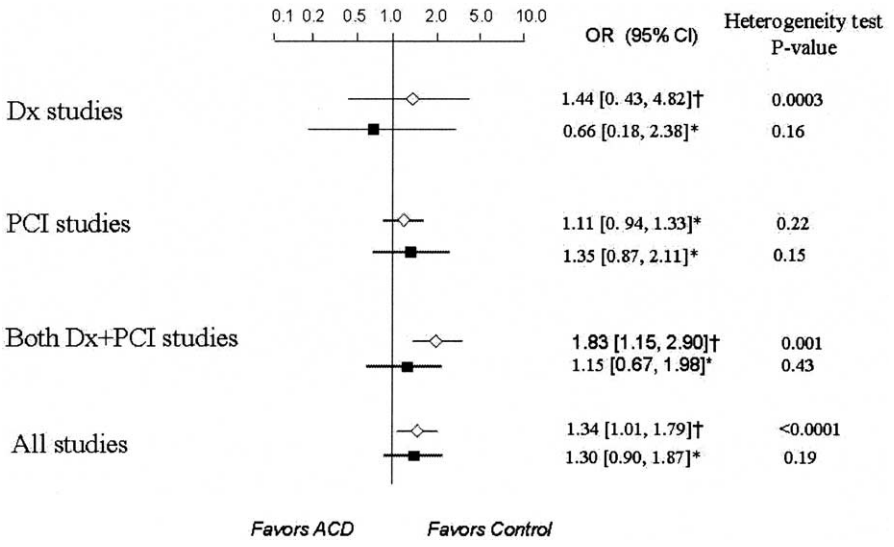

Figure 4. Odds ratio (OR) and 95% confidence interval (CI) of vascular access-related complication rate in patients with any arteriotomy closure device (ACD) and mechanical compression (control) in diagnostic (Dx), percutaneous coronary intervention (PCI), mixed, or any setting. **Diamonds** = all studies; **squares** = randomized studies.

peripheral arterial disease), operator (individual experience and learning curves for each device), and/or procedure (femoral artery puncture site, sheath size, first versus repeat procedure, level of anticoagulation before the vascular hemostasis, and the mode of adjunctive pharmacotherapy).

Finally, the different study methodologies may be an additional reason for the between-study heterogeneity. Specifically, the indications for and the timing of blood product transfusions were not specified in the included studies, but rather left to local standards of care. Diversity of methods for the diagnosis of complications (e.g., clinical only vs. ultrasound-guided approach) and different durations of follow-up are the obvious reasons for the difference in the obtained results. This is especially true with regard to assessing rates of hematomas. In the included studies, criteria for the definition of groin hematoma had a very wide range (Table 3). Taking this consideration into account, groin hematoma was not considered a primary end point.

There was no statistically significant heterogeneity in either diagnostic or PCI setting in the Angio-Seal and VasoSeal studies. As for Perclose, the studies were found to be heterogeneous only in the diagnostic setting. The following sources of heterogeneity in the latter studies were identified: patients in the study of Kahn et al. (34), favoring mechanical compression versus Perclose, were older and more frequently diabetic than patients in the study of Gerckens et al. (7), reporting similar rates of complications in both groups. The study by Duffin et al. (12), the third study in the diagnostic setting that also did not favor either mode of hemostasis, had longer duration of follow-up (30 days) than two previous studies (7,34) (in-hospital stay solely).

Remarkably, studies assessing vascular complications in the setting of mixed procedures (both diagnostic and PCI) or in any setting (diagnostic, PCI, and both) were shown to be significantly heterogeneous (except for VasoSeal trials). Such heterogeneity is probably attributed to the principal difference in main procedural characteristics (primarily different sheath size and anticoagulation regimen). Therefore, to avoid obvious heterogeneity, the proper assessment of any ACD versus traditional compression should be performed separately for the diagnostic and PCI setting, and each device, not the entire device entity, should be compared with mechanical compression.

Relationship to current literature. Our results should also be interpreted within the context of the recently published meta-analysis by Koreny et al. (14), assessing efficacy and safety of ACD in patients undergoing cardiac catheterization. Koreny et al. (14) incorporated data on about 4,000 patients from 30 randomized studies; ACD and mechanical compression were associated with similar risk of local complications. In the same publication, using intention-to-treat data solely, the risk of hematoma and pseudoaneurysm appeared to be higher using ACD.

Despite general methodologic similarity between the study by Koreny et al. and our study, several principal differences exist. First is the different approach in defining the access site-related complications. The definition given by the individual study author was used by Koreny et al. (14); the ambiguity of including hematoma was discussed in detail earlier, and inclusion of this complication in the meta-analysis is subject to the tremendous variability of hematoma definitions (and assessment) among the various studies. Second, no separate analysis on diagnostic and interventional procedures was presented by Koreny et al. (14); vascular complications are known to depend primarily on the procedure type, and the anticoagulation and sheath size differ a great deal between diagnostic and interventional procedures (1,2). Third, 12 of 30 studies analyzed by Koreny et al. (14) were reported in abstract form, which is

Table 3. Definition of Hematoma in Studies Included in the Meta-Analysis

Study (Ref.)	Definition of Hematoma
Amin et al. (11)	<5, ≥5 to 10, and ≥10 cm in diameter
Applegate et al. (21)	>10 cm in diameter
Assali et al. (23)	>5 cm in diameter
Baim et al. (31)	Hematoma was not included as an end point
Carere et al. (32)	<5, 5 to 10, and >10 cm in diameter
Carey et al. (19)	No definition of hematoma; hematoma was not included as an end point
Camenzind et al. (26)	<10, 10 to 20, and >20 cm in diameter
Chamberlin et al. (29)	Hematoma requiring blood transfusion or an extended hospital stay
Chevalier et al. (9)	>6 cm in diameter
Cremonesi et al. (17)	>6 cm, requiring surgical repair
Cura et al. (18)	≥5 cm in diameter
Dangas et al. (20)	Blood accumulation ≥2 × 4 cm or requiring transfusion or resulting in prolonged hospitalization
Duffin et al. (12)	Any significant hematoma reported by the cardiovascular nurse based on standard guidelines
Eidt et al. (22)	Hematoma sufficient to warrant surgical consultation
Gerckens et al. (7)	>4 cm in diameter
Gwechenberger et al. (5)	>6 × 6 cm
Kahn et al. (34)	Large hematoma: accumulation of subcutaneous blood ≥2 cm in diameter, small hematoma: <2 cm
Kornowski et al. (35)	≥10 cm in diameter
Kussmaul et al. (3)	Any palpable mass
Nasu et al. (10)	0.5 to 3 cm and >3 cm in diameter
Noguchi et al. (8)	Hematoma <5 or ≥5 cm in diameter
Rickli et al. (13)	Hematoma >1 ml on ultrasound examination
Sanborn et al. (25)	2 to 6 cm and >6 cm in diameter
Schickel et al. (30)	2 to 6 cm and > 6 cm in diameter
Schrader et al. (24)	>6 cm in diameter
Slaughter et al. (4)	2 to 6 cm and >6 cm in diameter
Silber et al. (28)	<7, 7 to 15, and >15 cm in diameter
Von Hoch et al. (27)	Hematoma was not included as a complication
Ward et al. (6)	<6 cm or ≥6 cm in diameter
Wetter et al. (33)	Hematoma >1 ml on ultrasound examination

not considered peer-reviewed publication. Though there is no consensus regarding this issue, we chose to include only published studies providing detailed information on methodology, end point definitions, and outcomes.

Other criteria for ACD assessment. In our study, we focused principally on the comparison of complication rates using ACD versus mechanical compression for hemostasis because this matter has been in debate (14). Other important aspects in the assessment of ACD include efficacy of the specific device, time to hemostasis, ambulation and discharge, patient viewpoint, and cost-effectiveness. The analyzed studies had a wide range of ACD failure (up to 20%); this is certainly an important consideration in the overall assessment of ACD, and it understandably improves with newer generations of devices and with operator experience.

The majority of the included studies demonstrated a reduced time to hemostasis and ambulation in both the diagnostic and PCI settings using ACD versus mechanical compression (3–10,12,13,23–25,28,31–33,35); the critical issue has been a potential tradeoff of safety with ACD use, as we suggested in our previous study with the very early ACD generations (20) and another recent meta-analysis has speculated (14). According to our present meta-analysis, no such concern appears justifiable for most ACD types.

Only a few studies have assessed patient viewpoint using a vascular closure device; this is because little dispute exists on the fact that ACD application does improve patient satisfaction and time to ambulation (8,10–13,30,32). Indeed, the majority of studies have reported that patient satisfaction was higher using ACD (Angio-Seal and Perclose) than mechanical compression (8,10–13,32); however, two studies showed no difference in the level of patient satisfaction using ACD (Perclose and VasoSeal) compared with manual compression (12,30). Only two studies demonstrated a reduction of in-hospital stay (8,10) and costs (8,13) using Perclose compared with mechanical compression.

Study limitations. Because of the specifics of the procedure to achieve hemostasis, blinding is not possible even in randomized trials of ACD. Relatively small percentages of women were included in the trials. This meta-analysis still covered publications mostly related to the early generations of ACD. Rapidly advancing device technologies may change the position of ACD compared to the conventional compression technique. Additional studies are required to examine the safety of ACD and the impact of generational advances of these devices on outcomes.

Conclusions. In the setting of Dx cardiac catheterization, the risk of vascular complications related to arterial access site was similar with all three devices when compared with mechanical compression. In the setting of PCI, Angio-Seal and Perclose were similar to mechanical compression. The rate of complications after PCI was higher with VasoSeal compared to mechanical compression. Despite inherent bias and differences in study designs, our meta-analysis may provide a helpful tool to understand the sources of variability in results across studies and to improve the design of future studies on ACD.

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APPENDIX

For a list of the studies excluded from the meta-analysis, please see the September 15, 2004, issue of *JACC* at www.cardiosource.com/jacc.html.