EuroIntervention

Expanded use of the TAXUS Express Stent: two-year safety insights from the 7,500 patient ARRIVE Registry programme

John M. Lasala[1]*, MD, PhD; David A. Cox[2], MD; Stephen J. Lewis[3], MD; Peter N. Tadros[4], MD; Robert C. Haas[5], MD; Marc J. Schweiger[6], MD; Anil Chhabra[7], MD; William J. Untereker[8], MD; Ruth M. Starzyk[9], PhD; Stephen R. Mascioli[9], MD; Keith D. Dawkins[9], MD; Donald S. Baim[9], MD for the ARRIVE 1 and ARRIVE 2 Participating Physicians

1. Washington University School of Medicine, St. Louis, MO, USA; 2. Lehigh Valley Hospital, Allentown, PA, USA; 3. Cardiology Centre of Cincinnati, Cincinnati, OH, USA; 4. Kansas University Hospital, Kansas City, KS, USA; 5. St. John Medical Centre, Tulsa, OK, USA; 6. Baystate Medical Centre and Tufts University School of Medicine, Springfield, MA, USA; 7. Willis Knighton Medical Centre, Shreveport, LA, USA; 8. University of Pennsylvania, Philadelphia, PA, USA; 9. Boston Scientific Corporation, Natick, MA, USA

Dr. Lasala declares Speakers Bureau fees and consulting fees from Boston Scientific Corporation (BSC) and Cordis. Dr. Cox declares Speakers Bureau fees and consulting fees from BSC, The Medicines Company and Abbott; Medical Advisory Board for BSC and Abbott. Drs Schweiger, Chhabra: Medical Advisory Board for BSC. Dr. Untereker is a stockholder of BSC and Cordis. Drs Starzyk, Mascioli, Dawkins and Baim are full time employees and stockholder of BSC. The remaining authors have no conflict of interest to declare.

KEYWORDS
Coronary disease, registries, restenosis, stents, expanded use of drug-eluting stents

Abstract

Aims: We report 2-year outcomes in a large unselected drug-eluting stent population (N=7,492) in the TAXUS Express[2] ARRIVE post-market surveillance programme (101 U.S. sites).

Methods and results: No specific inclusion/exclusion criteria were mandated; patients enrolled at procedure initiation. Two-year follow-up was 94%, with independent adjudication of major cardiac events, monitoring of patients with cardiac events and an additional 10-20% sample by site. Most ARRIVE cases (64%, n=4,794) typified expanded use based on patient/lesion characteristics outside the simple use (single vessel/stent) pivotal trial populations. These expanded use patients had higher 2-year rates than simple use patients for mortality (7.8% vs. 4.2%, P<0.001), myocardial infarction (MI, 3.9% vs. 2.2%, P<0.001), target lesion revascularisation (TLR, 9.2% vs. 5.4%, P<0.001), and stent thrombosis (3.3% vs. 1.4%, P<0.001). Among subgroups with renal disease, chronic total occlusion (CTO), lesion >28 mm, reference vessel diameter (RVD) <2.5 mm, multivessel stenting, acute MI, bifurcation, vein graft, or in-stent restenosis, TLR ranged from 3.8% to 8.9% in year one, and from 1.3% to 6.0% during year two.

Conclusions: Mortality and stent-related events were higher in expanded use than simple use patients in the pivotal trials. ARRIVE provides a detailed estimate of procedural and 2-year outcomes in such real-world patients.

** Corresponding author: Washington University School of Medicine, Cardiology, Campus Box 8086, 660 South Euclid Avenue, St. Louis, MO, USA 63110*

E-mail: jlasala@im.wustl.edu

Introduction

Randomised, controlled trials (RCT) have demonstrated a clear restenosis advantage of drug-eluting stents (DES) over bare-metal stents (BMS), with no significant difference in death or myocardial infarction (MI) in the generally uncomplicated patients/lesions studied in such trials.[1-4] However, the inherent homogeneity of RCT patients limits the ability to extrapolate their findings to routine practice that involves a broader range of clinical conditions and lesion types. The U.S. Food and Drug Administration (FDA) thus mandated as a condition for approval of the paclitaxel-eluting TAXUS™ Express²™ stent (PES) the systematic collection of data through 2-years among unselected patients. The TAXUS peri-AppRoval Registry: a multIcentre safety surVEillance (ARRIVE) programme was undertaken as a two-phase U.S. safety surveillance registry at 103 sites. With 2-year data on 7,492 patients, including 4,794 patients who would have been excluded from pivotal RCTs, ARRIVE allows detailed estimation of even low frequency stent related events in a real-world DES population.

Methods

Patient selection, device, study procedure

The two registries –FDA-mandated ARRIVE 1 and the voluntary post-market ARRIVE 2– were similarly designed to consecutively enrol patients, as described previously.[5] Both are registered on the National Institutes of Health website (Identifiers NCT00569491 and NCT00569751). Consecutive enrolment was defined as a commitment by ≥2 investigators at each facility to enrol all consented patients deemed appropriate for a DES. Patients provided informed consent under a protocol approved by the local institutional review board in conformity with the Declaration of Helsinki and FDA guidelines. No specific inclusion/exclusion criteria were mandated; all patients receiving a TAXUS stent were included, whether or not they also received a non-TAXUS stent during the index procedure. Each patient was enrolled at procedure initiation to minimise potential bias by exclusion for complicated or unsuccessful procedures. The TAXUS Express² PES (Boston Scientific Corporation [BSC], Natick, Massachusetts, USA) has been described previously.[6] Vessel size and lesion length were determined by visual estimate; stents were placed per the Directions For Use (DFU) and/or standard percutaneous coronary intervention (PCI) practices. Dual antiplatelet therapy (aspirin and clopidogrel/ticlopidine, DAPT) was begun before or immediately after the procedure. Aspirin was continued indefinitely with oral clopidogrel/ticlopidine recommended for six months per the DFU.

Data collection, monitoring, follow-up

Data, captured via web based reporting with predefined queries, were verified against source documents for all cardiac events. To encourage accuracy and completeness of data collection, sponsor (BSC) monitors assessed an additional 20% per site sampling of patients in ARRIVE 1 and 10% in ARRIVE 2. A Clinical Events Committee (CEC, Appendix 1 - online as supplementary data at www.eurointervention.org) independent of BSC determined the relationship of reported cardiac events to the study device. An event was considered "TAXUS-stent-related" if it occurred at the stented segment or if the relationship to the TAXUS stent could not be excluded based upon available information.

Study definitions are in Appendix 2 (online as supplementary data at www.eurointervention.org). Major cardiac events (MCE) included all cardiac death, MI, and target vessel revascularisation (TVR). Follow-up angiography was not mandated, and was performed in accordance with local practice. Target lesion revascularisation (TLR) was defined as "TAXUS-stent-related" TVR, given the absence of a central angiographic core laboratory. An independent committee at the Harvard Clinical Research Institute adjudicated stent thrombosis (ST) per the ARC definite/probable definitions.[7]

Statistical analysis

Statistical analyses were carried out using the CEC's assessment of "TAXUS-related" cardiac events. Analyses were assessed in a collaborative effort between the study principal and co-principal investigators and the sponsor. Patient, lesion, and procedural characteristics and event rates were analysed using descriptive statistics with SAS System Software, Version 8.0 or higher (SAS Institute, Cary, North Carolina, USA). Simple proportions with two-sided P values from Student t-test were used for continuous variables; chi-square test was used for noncontinuous variables. The Kaplan-Meier product method (log-rank P value) was used for time-to-event analyses. To identify predictors of major events at 2 years, 41 variables (Appendix 3 online as supplementary data at www.eurointervention.org) were assessed using backward Cox proportional hazards regression; the threshold to remain in the model was P=0.10.

Results

Patient, lesion, and procedural characteristics

Patients were enrolled February through May 2004 (ARRIVE 1) and October 2004 to October 2005 (ARRIVE 2). The two ARRIVE registries (Appendix 4 online as supplementary data at www.eurointervention.org)

Table 1. ARRIVE programme experience.

Measure	ARRIVE programme[a]		
Enrolled patients	7601		
Analysed patients[b]	7492		
ARRIVE 1	2487		
ARRIVE 2	5005		
1-Year follow-up	97.1% (7274/7492)		
2-Year follow-up	93.9% (7035/7492)		
	All patients	Simple use[a]	Expanded use[a]
Patients (N)	7,492	2,698	4,794
Lesions (N)	10,668	3,112	7,556
Vessels (N)	8,795	2,698	6,097
Stents (N)	11,883	3,273	8,610

Values are n or percent (count/sample size). [a] Statistical comparisons (baseline demographic and lesion data, procedural, and postprocedural characteristics) between ARRIVE 1 and ARRIVE 2 indicated data could be pooled. [b] 98 patients from two ARRIVE 1 sites were excluded from analysis due to non-compliance with Good Clinical Practice; 9 patients excluded from ARRIVE 2 due to simultaneous enrolment in another clinical trial; 2 excluded due to treatment with a TAXUS stent for a dissection rather than a primary event.

were designed to allow data pooling and tested for its appropriateness, and together comprised an analysis population of 7,492 patients (Table 1). Most ARRIVE cases (64%) were classified as expanded use (n=4,794, Figure 1) based on patient and/or lesion characteristics considered outside the simple use population studied in the TAXUS IV pivotal RCT.[3] Baseline characteristics and a comparison between simple and expanded use cohorts are shown in Table 2. Expanded use had statistically significantly more baseline comorbidities as well as more complex disease than simple use (Table 2). Characteristics of nine expanded use subgroups show the higher baseline risk associated with these patients (Table 3).

Outcomes in year 1 and year 2

Outcomes data were available for 97% and 94% of analysed patients at 1-year and 2-years, respectively. In year one, outcomes data were available for 7,274 patients and the 1-year per patient composite MCE rate was 9.5% (691/7274). This included cardiac death (2.2%, 159/7274), MI (2.1%, 155/7274), TVR (6.8%, 492/7274), and TLR (5.1%, 373/7274). In year two, outcomes data were available for 6,882 patients and MCE occurred in 4.7% (325/6882), consisting mostly of TVR (3.2%, 223/6882) with a TLR rate of 2.5% (172/6882). All-cause mortality was 3.5% (257/7274)

Table 2. Baseline characteristics of ARRIVE population, simple use cohort, and expanded use cohort.

Characteristic	All patients (N=7,492)	Simple use[a] (N=2,698)	Expanded use[a] (N=4,794)	P Value[b]
Patient characteristics				
Male	67.3% (5,043)	65.9% (1,777)	68.1% (3,266)	0.045
Age[c]	64.3±11.7	63.0±11.5	65.0±11.8	<0.001
Smoker at baseline	23.5% (1,764)	24.2% (652)	23.2% (1,112)	0.34
Hypercholesterolaemia	75.8% (5,677)	74.4% (2,007)	76.6% (3,670)	0.04
Hypertension	76.0% (5,691)	75.4% (2,034)	76.3% (3,657)	0.38
Diabetes mellitus (all)[d]	31.6% (2,368)	29.8% (805)	32.6% (1,563)	0.01
Oral medication	22.9% (1,718)	21.8% (589)	23.6% (1,129)	0.09
Insulin treated	10.2% (764)	8.9% (241)	10.9% (523)	0.007
Previous MI	36.3% (2,722)	26.9% (725)	41.7% (1,997)	<0.001
Previous stroke	6.2% (467)	5.0% (135)	6.9% (332)	0.001
Renal disease[e]	2.5% (191)	0.0%(0)	4.0% (191)	<0.001
Multivessel disease	36.9% (2,765)	27.1% (733)	42.4% (2,032)	<0.001
Previous CABG	20.1% (1,502)	11.4% (307)	25.0% (1,195)	<0.001
Previous PCI	36.8% (2,725)	34.5% (930)	37.4% (1,795)	0.009
Cardiogenic shock	0.4% (31)	0.0% (0)	0.6% (31)	<0.001
CHF[f]	6.8% (511)	5.0% (134)	7.9% (377)	<0.001
Left main disease	4.8% (359)	0.0% (0)	7.5% (359)	<0.001
Lesion characteristics[g]				
Mean RVD (mm)[h]	3.0±0.5 (10,665)	3.0±0.4 (3,110)	3.0±0.5 (7,555)	<0.001
Mean lesion length (mm)[h]	15.6±9.2 (10,630)	13.7±5.8 (3,103)	16.4±10.2 (7,527)	<0.001
B2/C lesion[h]	50.3% (5,360)	33.3% (1,035)	57.3% (4,324)	<0.001
Calcification[i]	18.2% (1937)	0.0% (0/3111)	25.6% (1937)	<0.001
Prior brachytherapy	0.4% (38)	0.0% (0)	0.5% (38)	<0.001
Procedural characteristics				
1 Vessel treated per patient	83.9% (6,284)	100.0% (2,698)	74.8% (3,586)	<0.001
1 Lesion treated per patient	68.0% (5,098)	86.5% (2,334)	57.7% (2,764)	<0.001
Stents per lesion[j]	1.1±0.4 (10,553)	1.1±0.2 (3,108)	1.2±0.5 (7,445)	<0.001
Stent length per lesion[j] (mm)	20.9±11.0 (10,553)	18.7±7.1 (3,108)	21.9±12.1 (7,445)	<0.001
Stents per patient[j]	1.6±0.9 (7,492)	1.2±0.5 (2,698)	1.80±1.0 (4,794)	<0.001
1	60.5% (4,536)	81.7% (2,205)	48.6% (2,331)	<0.001
2	26.3% (1,967)	15.6% (420)	32.3% (1,547)	<0.001
≥3	13.2% (989)	2.7% (73)	19.1% (916)	<0.001
Stent length per patient[j] (mm)	29.5±19.2 (7,492)	21.6±10.6 (2,698)	34.0±21.3 (4,794)	<0.001

Numbers are percent (n) or mean±SD (n). [a] Simple use and expanded use are defined in Figure 1. [b] P values are for the comparison between simple use and expanded use groups and are two-sided from Student t-test for continuous variables and from the chi-square test for binary proportions. [c] 1,462 patients (19.5%) were >75 years. [d] Among all ARRIVE patients with diabetes, 256 were not treated medically (oral agents and/or insulin); of 764 insulin-treated diabetic patients, 370 (48.4%) were also treated with oral agents. [e] Site reported as serum creatinine >3.0 mg/dL or patient on dialysis. [f] Site reported as NYHA Class ≥III. [g] Lesions: N=10,668 (all); N=3,112 (simple use); N=7,556 (expanded use) [h] Data reported per site visual estimate. [i] Moderate or severe calcification [j] TAXUS Express[2] stent; of 7,492 analysed patients, 95.9% (7187) received only TAXUS stents at index procedure. CABG: coronary artery bypass graft; CHF: congestive heart failure; PCI: percutaneous coronary intervention; MI: myocardial infarction; RVD: reference vessel diameter

Table 3. Baseline characteristics of ARRIVE expanded-use subgroups.

Characteristic	AMI	Lesion >28 mm	RVD <2.5 mm	Multivessel stenting[a]	Bifurcation lesion[b]	ISR	Vein graft	Renal disease[c]	CTO
Patients (N)	954	747	251	1208	575	489	474	191	161
Lesions (N)	1328	812	287	2969	741	546	578	284	182
Vessels (N)	1067	767	265	2511	597	501	524	225	165
Stents (N)	1537	1460	305	3262	842	627	706	330	251
Patient characteristics									
Male	66.6% (635)	69.1% (516)	58.6% (147)	67.4% (814)	69.4% (399)	70.1% (343)	80.8% (383)	64.9% (124)	76.4% (123)
Age	62.2±13.0	63.7±11.8	65.4±12.1	65.1±11.7	63.3±11.7	63.4±11.3	68.0±10.4	65.5±11.9	60.5±11.6
Smoker at baseline	36.2% (345)	25.4% (190)	23.5% (59)	21.6% (261)	24.3% (140)	20.9% (102)	12.4% (59)	14.1% (27)	28.6% (46)
Hyper-cholesterolaemia	59.7% (570)	78.3% (585)	72.1% (181)	78.8% (952)	76.5% (440)	92.0% (450)	88.6% (420)	71.7% (137)	75.2% (121)
Hypertension	63.9% (610)	73.2% (547)	74.5% (187)	77.8% (940)	76.7% (441)	82.2% (402)	79.7% (378)	95.3% (182)	73.9% (119)
Diabetes mellitus (all)	24.6% (235)	33.2% (248)	40.2% (101)	36.3% (439)	29.4% (169)	36.0% (176)	40.3% (191)	62.3% (119)	24.8% (40)
Oral medication	16.2% (155)	24.0% (179)	29.1% (73)	27.9% (337)	20.0% (115)	26.0% (127)	29.5% (140)	29.8% (57)	13.7% (22)
Insulin treated	8.8% (84)	11.2% (84)	17.1% (43)	11.3% (137)	9.9% (57)	14.7% (72)	15.0% (71)	33.0% (63)	9.9% (16)
Previous MI	67.1% (640)	42.3% (316)	36.3% (91)	37.8% (457)	36.9% (212)	51.3% (251)	48.9% (232)	46.1% (88)	39.8% (64)
Previous stroke	6.1% (58)	8.4% (63)	5.6% (14)	7.1% (86)	5.9% (34)	7.6% (37)	10.3% (49)	15.2% (29)	1.2% (2)
Renal diseasec	0.9% (9)	3.3% (25)	1.6% (4)	2.6% (31)	1.9% (11)	3.7% (18)	3.8% (18)	100% (191)	1.2% (2)
Multivessel disease	25.8% (246)	44.7% (334)	39.8% (100)	52.5% (634)	40.9% (235)	53.8% (263)	72.2% (342)	55.0% (105)	35.4% (57)
Previous CABG	10.2% (97)	20.3% (152)	23.5% (59)	21.4% (258)	16.4% (94)	32.3% (158)	100% (474)	26.2% (50)	18.0% (29)
Previous PCI	20.4% (195)	36.5% (273)	35.5% (89)	33.5% (405)	38.4% (221)	96.5% (472)	48.1% (228)	35.6% (68)	24.8% (40)
Cardiogenic shock	2.0% (19)	0.8% (6)	0.8% (2)	0.3% (4)	1.0% (6)	0.4% (2)	0.4% (2)	0.5% (1)	0.6% (1)
CHF[d]	5.2% (50)	9.4% (70)	8.4% (21)	7.3% (88)	7.7% (44)	8.0% (39)	9.1% (43)	24.1% (46)	4.3% (7)
Left main disease	3.2% (31)	4.1% (31)	5.6% (14)	7.3% (88)	6.1% (35)	6.7% (33)	15.2% (72)	8.9% (17)	5.6% (9)
Lesion characteristics									
RVD (mm)[e]	3.1±0.5 (1328)	3.0±0.4 (812)	2.2±0.2 (287)	3.0±0.4 (2968)	2.9±0.4 (741)	3.1±0.5 (546)	3.3±0.5 (578)	3.0±0.5 (284)	2.9±0.4 (182)
Lesion length (mm)[e]	16.6±9.5 (1321)	37.9±12.1 (812)	14.9±10.9 (286)	15.6±9.2 (2955)	15.3±8.9 (737)	17.7±11.3 (546)	16.7±12.6 (575)	15.8±10.3 (284)	24.8±17.5 (180)
B2/C lesion	58.9% (781)	79.8% (648)	50.5% (145)	51.0% (2965)	69.2% (513)	56.2% (307)	58.3% (337)	49.6% (141)	93.4% (170)
Calcification-moderate/severe	14.2% (189)	28.1% (228)	18.8% (54)	19.9% (591)	20.8% (154)	16.3% (89)	7.3% (42)	28.5% (81)	22.0% (40)
Procedural characteristics									
1 Vessel treated per patient	89.5% (854)	97.3% (728)	94.4% (237)	N/A	96.3% (553)	97.5% (477)	89.7% (425)	82.8% (423)	97.5% (157)
1 Lesion treated per patient	69.4% (662)	92.1% (688)	88.4% (222)	N/A[f]	73.4% (422)	89.4% (437)	81.0% (384)	66.5% (127)	87.6% (141)
Stents per lesion[g]	1.2±0.5 (1321)	1.8±0.8 (804)	1.1±0.5 (270)	1.1±0.4 (2911)	1.2±0.5 (732)	1.2±0.5 (538)	1.2±0.6 (576)	1.2±0.5 (283)	1.4±0.8 (180)
Stent length per lesion[g] (mm)	22.6±11.3 (1321)	43.5±17.8 (804)	19.6±14.0 (270)	20.9±10.7 (2911)	21.0±11.0 (732)	23.6±13.6 (538)	24.0±16.7 (576)	21.1±12.2 (283)	32.4±23.0 (180)
Stents per patient[g]	1.6±0.9 (954)	2.0±0.9 (741)	1.3±0.7 (236)	2.7±1.0 (1208)	1.5±0.7 (572)	1.3±0.6 (485)	1.5±0.9 (473)	1.7±1.1 (191)	1.6±0.9 (159)
1	57.7% (550)	30.1% (225)	76.1% (191)	3.0% (36)	63.5% (365)	77.1% (377)	67.1% (318)	59.2% (113)	62.7% (101)
2	28.9% (276)	49.7% (371)	12.0% (30)	51.2% (619)	27.7% (159)	16.8% (82)	21.9% (104)	20.4% (39)	21.7% (35)
≥3	13.4% (128)	19.4% (145)	6.0% (15)	45.8% (553)	8.3% (48)	5.3% (26)	10.8% (474)	20.4% (39)	15.5% (25)
Stent length per patient[g] (mm)	31.2±18.6 (954)	46.9±19.4 (741)	22.5±17.5 (236)	50.3±23.7 (1,208)	26.8±14.9 (572)	26.2±16.1 (485)	29.3±21.0 (473)	31.2±20.9 (191)	36.7±25.3 (159)

Numbers are percent (n) or mean±SD (n); [a] 2 vessels were treated in 92.5% (1117) of patients; [b] 63.5% of patients with a bifurcation lesion were treated with a single stent; [c] Site reported as serum creatinine >3.0 mg/dL or patient on dialysis; [d] Site reported as NYHA Class ≥III; [e] Data reported per site visual estimate; f: 2 lesions were treated in 66.6% (804) of patients; [g] TAXUS stents; AMI: acute myocardial infarction (patient presented with STEMI/NSTEMI); CABG: coronary artery bypass graft; CTO: chronic total occlusion (site reported); ISR: in-stent restenosis; N/A: not applicable; PCI: percutaneous coronary intervention; RVD: reference vessel diameter

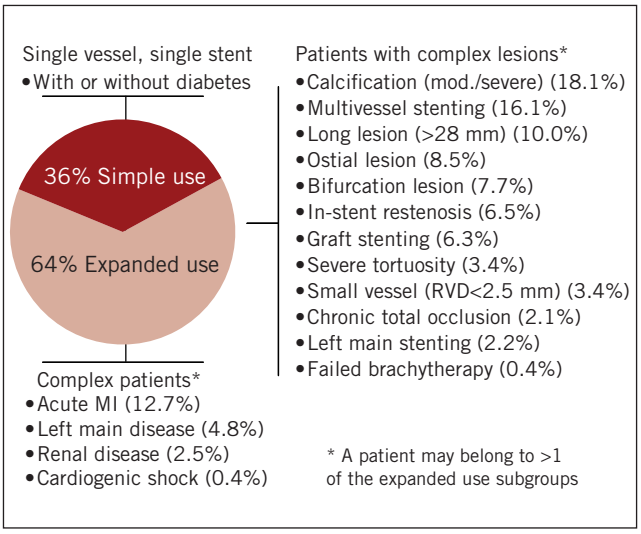

Figure 1. Usage patterns in ARRIVE (N=7492). Simple use cases excluded one or more of the following: acute myocardial infarction (AMI); bifurcation, cardiogenic shock, chronic total occlusion, prior brachytherapy, vein graft stenting, in-stent restenosis, large vessel (RVD>3.75 mm), left main disease/stenting, long lesion (>28 mm), moderate/severe calcification, multivessel stenting (mean of 2.1 vessels per patient), ostial lesion, renal disease (serum creatinine >3.0 mg/dL or dialysis), severe tortuosity, small vessel (RVD<2.5 mm). Expanded use cases are those not classified as simple use.

in year one and 3.0% (204/6882) in year two, with low rates of year two cardiac death (1.5%, 101/6882) and MI (1.1%, 74/6882). Stent thrombosis was 1.8% (128/7274) during year one and 0.8% (56/6882) in year two; at physician discretion 67.7% of patients received DAPT through 1-year, 53.1% through 2-years.

Diabetes status was determined by the investigative sites and 2,368 (31.6%) of all ARRIVE patients were considered diabetic. Medically treated (oral medications and/or insulin) diabetic patients made up 89.2% (2112/2368) of the ARRIVE diabetic population and outcomes data were available for 2,049 medically treated patients in year one and 1,900 in year two. These medically treated diabetic patients had a 1 year composite MCE rate of 10.7% (220/2049) with a TLR rate of 4.8% (98/2049). In year two, their composite MCE rate was 6.6% (125/1900), with 3.1% TLR (59/1900). A detailed discussion of ARRIVE diabetic patients is the subject of a separate manuscript.[8]

Outcomes in expanded use subgroups

The ARRIVE expanded use cohort had significantly higher 2-year MCE rates compared to the simple use group (Figure 2). The most common event was revascularisation. Rates for early ST (≤30 days) were >3-fold higher for expanded use (1.4% vs. 0.4%). Differences between incidence curves are evident before 30 days and continue through 2-years.

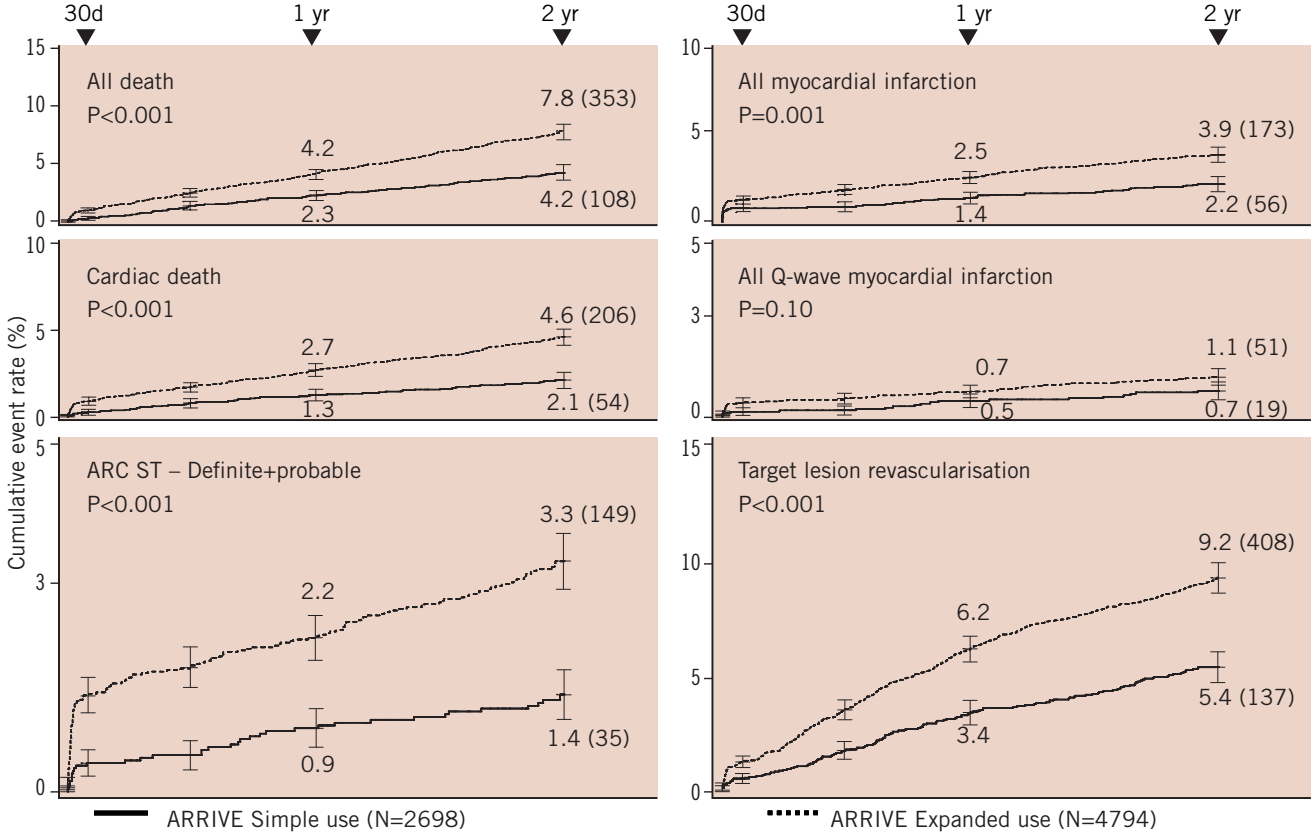

Figure 2. Comparison of event rates through 2-years in simple use and expanded use subgroups in ARRIVE. Definitions of simple use and expanded use are provided in Figure 1. ARC ST definite/probable definitions are from Cutlip et al[7]. Target lesion revascularisation was defined as "TAXUS-stent-related" target vessel revascularisation, given the absence of a central angiographic core laboratory. P value is log-rank; error bars are ±1.5SE. ARC: Academic Research Consortium; ST: stent thrombosis.

Mortality and ST were usually higher in year one than year two for the simple use and nine expanded use subgroups; only subgroups with vein grafts and small vessels had higher death rates in year two (Table 4). Renal disease patients (serum creatinine >3.0 mg/dL or dialysis) had more very late ST (VLST) in the second year and the highest combined rate for all death and MI (35.3%) through 2-years, significantly higher than the 6.0% rate in simple use patients (P <0.001, Figure 3).

Rates for Q-wave MI in year one were highest among patients with long lesions (>28 mm), small vessels (RVD <2.5 mm), and multivessel stenting (mean of 2.1 vessels per patient) while the acute myocardial infarction (AMI) subgroup was below the 0.5% simple use rate (Figure 4). During year two most expanded use subgroups had higher Q-wave MI rates than simple use (0.3%) except small vessel, renal disease, and CTO, which had no events. Figure 5 shows all expanded use subgroups had higher first year rates for TLR than simple use (3.4%). In year two rates were lower than year one for all subgroups except CTO. The AMI and small vessel subgroups had year two rates below that of simple use (1.9%).

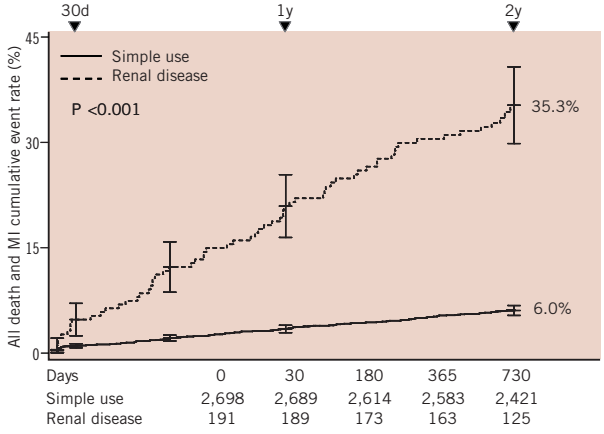

Figure 3. Comparison of Kaplan-Meier curves for combined all death and myocardial infarction between the ARRIVE simple use subgroup and the renal disease subgroup. Simple use and renal disease are defined in Figure 1. P value is log-rank; error bars are ±1.5SE.

Multivariate predictors of adverse events

Table 5 shows multivariate predictors for accumulated events over the two years of the registry, including all death, cardiac death, MI, and TLR. Renal disease was a strong predictor of death (3.4-fold increased risk), cardiac death (3.0-fold), and MI (1.8-fold). Other strong baseline predictors of death included cardiogenic shock (3.4-fold) and discontinuation of thienopyridine therapy before six (2.7-fold) or 12 months (3.0-fold). Expanded use patients generally had an increased risk of death, cardiac death, or MI (1.3 to 3.6-fold per factor) and complex lesion characteristics increased TLR risk (1.3 to 1.8-fold per factor). Multivariate ST predictors included early discontinuation of thienopyridine therapy, baseline smoking, vessel RVD <3.0 mm, prior brachytherapy, renal disease (>3-fold increased risk each) and others. A detailed discussion of ST and its predictors in ARRIVE is the subject of a separate manuscript.[9]

Discussion

The ARRIVE programme captured usage patterns and 2-year outcomes of the TAXUS Express[2] stent in 7,492 patients treated during routine practice. Event rates were generally higher in year one than year two. Simple use cumulative mortality rates through one and two years mirrored those of similar patients enrolled in the RCT TAXUS arm (2.0%; 3.4%)[5], validating the high degree of event ascertainment in the ARRIVE programme. Notwithstanding some overlap among patient subsets, analysis of nine specific ARRIVE

Table 4. Mortality and stent thrombosis in year 1 and year 2 in overall ARRIVE population and subgroups.

				Expanded-use subgroups								
Event	All patients	Simple use[a] (N=2,698)	Expanded use[a] (N=4,794)	AMI (N=953)	Lesion >28 mm (N=748)	RVD <2.5 mm (N=251)	Multivessel stenting[b] (N=1,208)	Bifurcation[c] (N=574)	ISR (N=489)	Vein graft (N=474)	Renal disease[d] (N=191)	CTO (N=161)
Year 1 (0–365 D)	N=7,274	N=2,623	N=4,651	N=904	N=722	N=240	N=1,174	N=557	N=479	N=465	N=184	N=153
All death	3.5% (257)	2.3% (60)	4.2% (197)	3.9% (35)	4.7% (34)	3.3% (8)	4.3% (51)	5.0% (28)	4.4% (21)	5.2% (24)	19.0% (35)	2.0% (3)
Cardiac	2.2% (159)	1.3% (33)	2.7% (126)	2.7% (24)	3.5% (25)	2.5% (6)	2.9% (34)	3.6% (20)	3.1% (15)	3.4% (16)	12.5% (23)	2.0% (3)
Noncardiac	1.3% (98)	1.0% (27)	1.5% (71)	1.2% (11)	1.2% (9)	0.8% (2)	1.4% (17)	1.4% (8)	1.3% (6)	1.7% (8)	6.5% (12)	0.0% (0)
ST[e]	1.8% (128)	0.9% (24)	2.2% (104)	2.7% (24)	4.0% (29)	3.3% (8)	2.8% (33)	2.9% (16)	2.1% (10)	2.4% (11)	1.6% (3)	2.6% (4)
Year 2 (366–730 D)	N=6,882	N=2,520	N=4,362	N=843	N=674	N=225	N=1,088	N=518	N=450	N=435	N=147	N=149
All death	3.0% (204)	1.9% (48)	3.6% (156)	2.8% (24)	4.3% (29)	4.0% (9)	3.1% (34)	2.5% (13)	4.0% (18)	6.0% (26)	17.0% (25)	1.3% (2)
Cardiac	1.5% (101)	0.8% (21)	1.8% (80)	1.3% (11)	1.6% (11)	1.8% (4)	1.6% (17)	1.3% (7)	2.4% (11)	3.7% (16)	8.8% (13)	1.3% (2)
Noncardiac	1.5% (103)	1.1% (27)	1.7% (76)	1.5% (13)	2.7% (18)	2.2% (5)	1.6% (17)	1.2% (6)	1.6% (7)	2.3% (10)	8.2% (12)	0.0% (0)
ST[e]	0.8% (56)	0.4% (11)	1.0% (45)	1.1% (9)	1.8% (12)	0.0% (0)	1.5% (16)	1.5% (8)	1.8% (8)	2.3% (10)	2.7% (4)	2.0% (3)

Numbers are binary rates, % (n). [a] Simple use and expanded use are defined in Figure 1. A patient may belong to more than one expanded-use subgroup. Year 2 rates (binary) differ slightly from those in Figure 2, which were calculated by the Kaplan-Meier product method. [b] Mean of 2.1 vessels per patient [c] 63.5% of patients were treated with a single stent [d] Site reported as serum creatinine >3.0 mg/dL or patient on dialysis [e] Per ARC definite/probable definitions[7]; AMI: acute myocardial infarction (patient presented with STEMI/NSTEMI); CTO: chronic total occlusion (site reported); D: days; ISR: in-stent restenosis; RVD: reference vessel diameter; ST: stent thrombosis

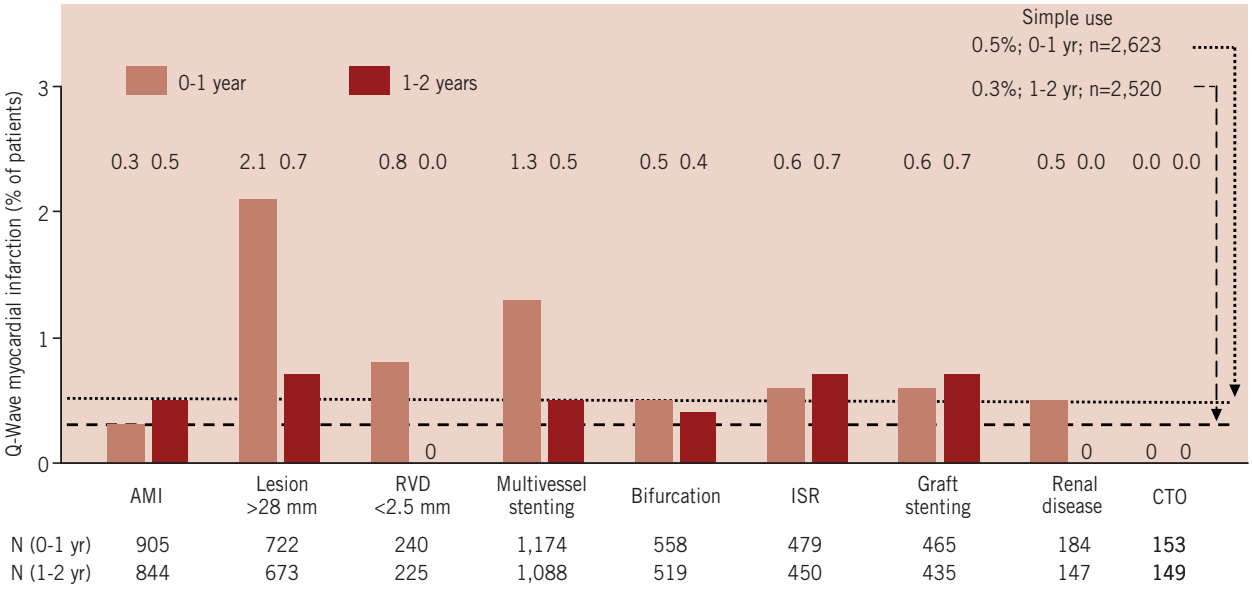

Figure 4. Q-wave myocardial infarction in ARRIVE expanded use subgroups at 1-year and 2-years. Event rates presented here were calculated as simple proportions. Rates for simple use (defined in Figure 1) differ slightly from those in Figure 2, which were calculated by the Kaplan-Meier product method. AMI: acute myocardial infarction; CTO: chronic total occlusion; ISR: in-stent restenosis; RVD: reference vessel diameter.

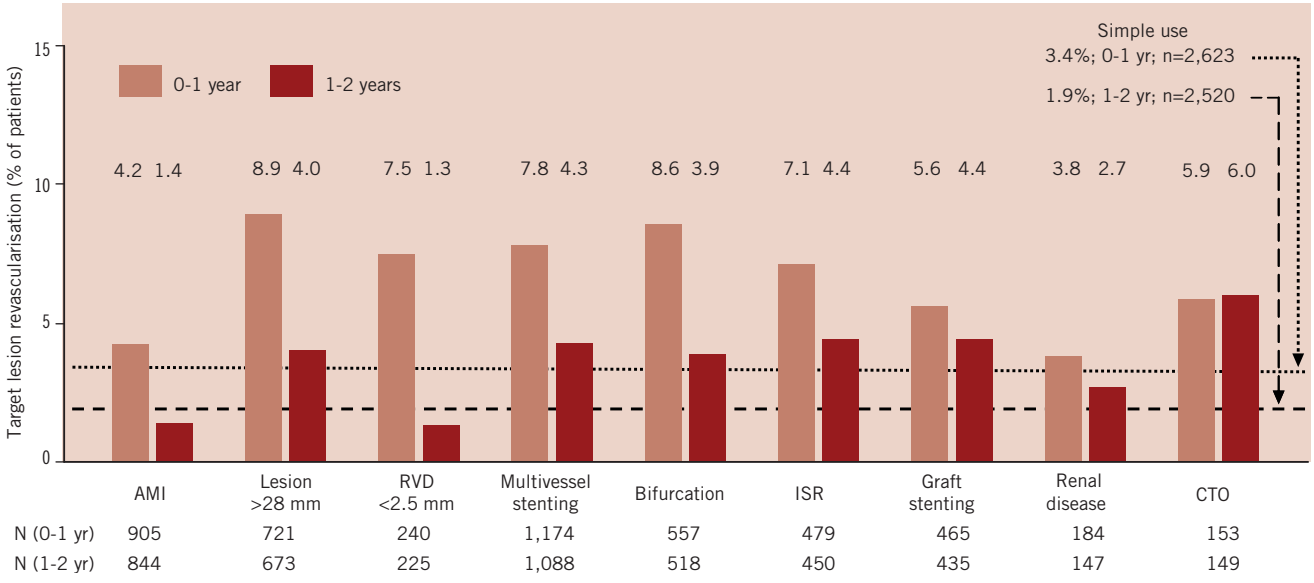

Figure 5. Target lesion revascularisation in ARRIVE expanded use subgroups at 1-year and 2-years. Target lesion revascularisation (TLR) was defined as "TAXUS-stent-related" target vessel revascularisation, given the absence of a central angiographic core laboratory. Event rates presented here were calculated as simple proportions. Rates for simple use (defined in Figure 1) differ slightly from those in Figure 2, which were calculated by the Kaplan-Meier product method. AMI: acute myocardial infarction; CTO: chronic total occlusion; ISR: in-stent restenosis; RVD: reference vessel diameter

expanded use subgroups provide insight into treatment and outcomes of such high-risk patients.

Outcomes in routine practice-overall population

ARRIVE event rates remained consistent with those of a revascularised broad coronary disease population through 2-years. Mortality (3.5% in year one and 3.0% in year two) was similar to that reported for the National Heart, Lung, and Blood Institute Dynamic Registry (NHLBI),[10] and the REAL, Ontario, and STENT registries.[11-13] While ARRIVE ST rates (1.8% in year one; 0.8% in year two) were higher than that reported for STENT through 2-years (1.5% for off-label DES use), they were similar to the 18 month ST rate of 2.9% for PES reported in the SORTOUT II randomised trial[14] that enrolled patients from everyday clinical practice. The initial concentration of ST in the first 30 days has been observed in other DES registries[13,15,16] and with BMS treatment[17] of complex lesions. Data from ARRIVE and other large, multicentre registries provide practical estimates of event rates in DES patients for expanded use indications. This is highly relevant to clinical practice since "off-label" DES use (ST elevation MI, in-stent restenosis [ISR], bypass grafts, and CTO) accounted for 21.4% of the >400,000 DES procedures in the American College of Cardiology National

Table 5. Multivariate predictors of ARRIVE major events at 2-years.

	Hazard ratio [95% confidence interval][a]			
Variable	**All death**	**Cardiac death**	**Myocardial infarction**	**Target lesion revascularisation[b]**
Cardiogenic shock	3.42 [1.61, 7.27]	NS	NS	NS
Renal disease	3.39 [2.54, 4.53]	3.03 [2.07, 4.44]	1.77 [0.98, 3.22]	NS
Thienopyridine discontinued before 12 months[c]	2.97 [2.30, 3.84]	2.45 [1.71, 3.52]	NS	0.74 [0.62, 0.90]
Thienopyridine discontinued before 6 months[d]	2.66 [2.11, 3.35]	3.32 [2.40, 4.61]	1.73 [1.27, 2.35]	NS
Left main stenting	2.27 [1.54, 3.37]	2.06 [1.22, 3.49]	NS	NS
Congestive heart failure	2.12 [1.65, 2.72]	2.68 [1.96, 3.67]	NS	NS
Stroke previous	1.64 [1.26, 2.15]	1.45 [1.01, 2.09]	NS	NS
MI previous	1.44 [1.19, 1.75]	1.69 [1.31, 2.17]	1.51 [1.16, 1.97	NS
Diabetes-insulin	1.44 [1.12, 1.86]	1.51 [1.09, 2.09]	1.58 [1.09, 2.27]	NS
Lesion calcification (moderate and severe)	1.43 [1.15, 1.78]	1.43 [1.07, 1.90]	1.32 [0.97, 1.79]	NS
Vein graft stenting	1.43 [1.05, 1.96]	1.61 [1.09, 2.37]	1.86 [1.18, 2.94]	1.76 [1.30, 2.39]
Multivessel disease	1.27 [1.04, 1.55]	NS	1.48 [1.13, 1.95]	NS
PCI previous	1.25 [1.02, 1.52]	NS	NS	1.28 [1.06, 1.54]
Lesion type B2 or C	1.23 [1.00, 1.50]	1.39 [1.06, 1.83]	NS	NS
Hypercholesterolaemia[e]	0.76 [0.61, 0.94]	NS	NS	NS
Age <70 years	0.51 [0.42, 0.61]	0.67 [0.52, 0.86]	1.30 [0.95, 1.78]	1.55 [1.27, 1.88]
Prior brachytherapy	NS	3.59 [1.28, 10.04]	NS	NS
Hypertension[e]	NS	1.55 [1.09, 2.20]	NS	NS
Ostial lesion	NS	1.40 [1.00, 1.97]	1.39 [0.94, 2.05]	1.40 [1.08, 1.80]
Lesion length >28 mm	NS	NS	2.08 [1.51, 2.87]	1.45 [1.12, 1.88]
Smoking at baseline	NS	NS	2.05 [1.54, 2.72]	NS
RVD <3 mm	NS	NS	1.72 [1.31, 2.25]	1.31 [1.10, 1.57]
LAD as target vessel	NS	NS	1.43 [1.08, 1.88]	1.41 [1.18, 1.68]
Postprocedure dilatation	NS	NS	1.33 [1.02, 1.73]	NS
ISR stenting	NS	NS	NS	1.49 [1.12, 1.98]
Multiple stents per lesion	NS	NS	NS	1.45 [1.19, 1.77]
Bifurcation	NS	NS	NS	1.43 [1.10, 1.87]
Preprocedure TIMI=0[f]	NS	NS	NS	1.37 [1.00, 1.87]
Multiple overlapping stents	NS	NS	NS	1.28 [0.98, 1.66]
Gender, male	NS	NS	NS	0.75 [0.63, 0.90]
AMI	NS	NS	NS	0.73 [0.54, 0.98]

Hazard ratios were assessed with the Cox proportional hazards regression model; 41 baseline variables were entered (Appendix 2) and backward selection was used; the threshold to stay in the model was set at 0.10; N=7492 patients in the ARRIVE population. [a] All values were significant at the P<0.05 level [b] TAXUS-stent-related target vessel revascularisation; [c] Patient was not receiving clopidogrel/ticlopidine at the 12-month visit; [d] Patient was not receiving clopidogrel/ticlopidine at the 6-month visit. [e] Patient was reported as having this condition and may or may not have been receiving medication for it; [f] AMI patients; AMI: acute myocardial infarction (patient presented with STEMI/NSTEMI); CABG: coronary artery bypass graft; ISR: in-stent restenosis; LAD: left anterior descend artery; MI: myocardial infarction; NS: not significant; PCI: percutaneous coronary intervention; RVD: reference vessel diameter; TIMI: thrombolysis in myocardial infarction

Cardiovascular Data Registry for 2003-2004.[18] Differences in the definition of "off-label" notwithstanding, ARRIVE's 64% expanded use rate is similar to DEScover (47%),[19] EVENT (55%),[15] NHLBI (49%),[20] and STENT (59%).[13] As confirmed in ARRIVE, expanded use DES patients had significantly higher 1-year rates versus simple use for death, TVR, and ST in DEScover,[19] more TLR and ST in EVENT,[15] higher 1-year rates for death, MI, and revascularisation in NHLBI,[20] and higher event rates through 2-years in STENT.[13] Such differential outcomes have also been reported for sirolimus-eluting stent-treated populations.[21]

Comparisons of outcomes with DES and BMS have evaluated the use of DES in off-label use collectively and in select subgroups.[11-13,20,22,23] Through 2-years, off-label DES use had a significantly lower TVR risk than BMS with a similar safety profile in NHLBI[20] and among 3,751 pairs of propensity score matched patients in the Ontario registry.[12] Mortality, MI, and TVR were also lower at nine months with off-label use of DES versus BMS in STENT, though the significant TVR advantage diminished by 2-years.[13] Mortality through 4-years was significantly lower with DES compared to BMS in a single-centre study of 8,032 patients undergoing PCI in 2003–2007.[22]

Outcomes in high risk subgroups

The large size of ARRIVE allowed for adequate numbers of specific high risk subgroups. Though many overlap, their analysis can provide insight into current use as well as outcomes and help physicians estimate likely clinical outcomes for individual patients. In evaluating expanded use patients, one notes that many would be poor candidates for BMS due to high restenosis rates and more likely to be treated by coronary artery bypass grafting (CABG). In the ARRIVE multivessel stenting subgroup, repeat revascularisation (7.8% in year one; 4.3% in year two) was higher than that reported for patients undergoing CABG in the New York State (U.S.) registry (5.1% at 18 months) but 1-year mortality (4.3%) was comparable to similar registry patients (4.2% for 2-vessel disease)[24] and to patients in the CABG arm of the SYNTAX RCT (3.4%).[25]

ARRIVE outcomes tended to mirror earlier reports on select subsets. Among AMI patients, mortality (3.9% in year one; 2.8% in year two) and revascularisation (4.2% in year one; 1.4% in year two) were lower than that reported for similar patients in STENT (8.0% death and 8.0% TVR through 2-years),[26] and a multicentre Massachusetts (USA) registry (10.7% death and 9.6% TVR through 2-years),[27] but comparable to a single centre report.[28] In the ARRIVE bifurcation subgroup, 2-year mortality was comparable to STENT[13]; year one cardiac death was higher (3.6% vs. 2.0%) and TLR rates lower (8.6% vs. 15.3%) than PES rates in a small multicentre European registry.[29] Mortality in ARRIVE compared to STENT was somewhat higher among patients with long (>28 mm) lesions and similar for patients receiving stents for ISR or CTO.[13] Treatment of CTOs with PES (N=48) has been shown to significantly reduce 1-year MACE and restenosis rates compared to matched cases treated with BMS.[30] Unlike the other eight ARRIVE subgroups, however, CTO subgroup TLR rates did not drop over time, as has also been reported for SES.[31] Low revascularisation and high mortality in ARRIVE renal disease patients echoed other reports, including NHLBI where 1-year mortality was lower in those patients treated with DES than BMS.[32,33]

Mortality increased from year one to year two among ARRIVE patients receiving stents for vein grafts (5.2% vs. 6.0%) or small (<2.5 mm) vessels (3.3% vs. 4.0%). Among vein graft patients, 2-year mortality was also high in STENT (8.8% at 2-years).[13] With the sirolimus-eluting stent little difference has been reported between DES and BMS in long-term outcomes in vein graft stenting, despite possible increased late events.[34-36] However, in the recently reported stenting of saphenous vein grafts RCT (BMS vs. PES, N=80), during a median follow-up period of 1.5 years PES were associated with significantly lower rates of angiographic restenosis, TLR, and target vessel failure.[37] While small vessel size generally has not increased the risk of death or MI, it has been reported to increase revascularisation.[38] In the ARRIVE small vessel group, 1-year TLR rates (7.5%) were lower than reported 9 month rates among PES patients with RVD <2.41 mm (16.4%) or RVD >2.41 and <2.84 mm (9.7%) in a single-centre DES registry,[38] and small vessel TLR in year 2 (1.3%) was the lowest of all ARRIVE subgroups, including simple use (1.9%).

Multivariate predictors of clinical events

Several characteristics of ARRIVE, including recruitment from multiple centres, specific predefined event definitions, use of a CEC, adequate independent monitoring, 2-year follow-up, and inclusion of all DES patient subsets allowed development of event predictors with substantial power. Renal disease was a strong (3.4-fold increased risk) independent predictor of mortality along with several other comorbid clinical factors, as reported by others.[23,28,39] Early discontinuation of thienopyridine therapy was associated with increased mortality through two years in ARRIVE as also shown by Eisenstein et al who found mortality to be lowest among patients remaining on clopidogrel for at least one year.[40] Iakovou et al[41] identified early discontinuation of antiplatelet therapy as a predictor of early and late ST, as seen also in ARRIVE. Predictors of revascularisation in ARRIVE included lesion related factors similar to other studies.[11,42] Awareness of the range of rates and significant predictors of MCE in DES registries may help physicians estimate individual patient outcomes and tailor treatment regarding choice of stent and follow-up regimen.

Study limitations

ARRIVE has some of the limitations common to registries, including absence of a control group, use of site visual assessments of angiographic data, absence of serial cardiac enzyme or electrocardiographic measurements that could underestimate the rate of smaller (non-Q) MI, and less monitoring than standard for traditional RCTs. Absent angiographic core laboratory evaluation, we cannot be certain that site reported "TLR" in the more extensive lesion subgroups fully excluded revascularisation events driven by progressive disease outside of the stented segment.[43] However, the close concordance between ARRIVE and RCT rates supports the premise that a real-world registry with this level of monitoring can provide reliable ascertainment of critical adverse events during two years of follow-up after DES treatment and may be the only source of such information for the many complex patient subgroups that have not undergone RCT evaluation.

Conclusions

The ARRIVE registries capture the broad spectrum of disease routinely treated by percutaneous coronary intervention including 4,794 (64%) expanded use cases outside the patient/lesion characteristics studied in pivotal RCTs. Rates for mortality and stent related events are expectedly higher in the expanded use cohort, and provide a valuable estimate of procedural and 2-year outcomes in such patients pending completion of ongoing RCTs.

Acknowledgments

The authors thank Yun Lu, M.S.; Kevin Najarian, M.S.; and Aijun Song, M.S. (BSC) for assistance with statistical analyses.

References

1. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med.* 2007;356:998-1008.

2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-23.

3. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350:221-31.

4. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation.* 2006;114:798-806.

5. Lasala JM, Cox DA, Dobies D, Muhlestein JB, Katopodis JN, Revtyak G, Baim DS. Usage patterns and 2-year outcomes with the TAXUS Express stent: Results of the US ARRIVE 1 registry. *Catheter Cardiovasc Interv.* 2008;72:433-45.

6. Abizaid A, Chan C, Lim YT, Kaul U, Sinha N, Patel T, Tan HC, Lopez-Cuellar J, Gaxiola E, Ramesh S, Rodriguez A, Russell ME. Twelve-month outcomes with a paclitaxel-eluting stent transitioning from controlled trials to clinical practice (the WISDOM Registry). *Am J Cardiol.* 2006;98:1028-32.

7. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

8. Lasala J, Cox D, Morris D, Breall J, Mahoney P, Horwitz P, Shaw D, Hood K, Mandinov L, Dawkins K. Two-year results of paclitaxel-eluting stents in patients with medically treated diabetes mellitus from the TAXUS ARRIVE program. *Am J Cardiol.* 2009;in press.

9. Lasala JM, Cox DA, Dobies D, Baran K, Bachinsky WB, Rogers E, Breall JA, Lewis DH, Song A, Starzyk RM, Mascioli SM, Dawkins KDD, Baim DS. Drug-eluting stent thrombosis in routine clinical practice: 2 year outcomes and predictors from the TAXUS ARRIVE registries. *Circ Cardiovasc Intervent.* Submitted.

10. Abbott JD, Voss MR, Nakamura M, Cohen HA, Selzer F, Kip KE, Vlachos HA, Wilensky RL, Williams DO. Unrestricted use of drug-eluting stents compared with bare-metal stents in routine clinical practice: findings from the National Heart, Lung, and Blood Institute Dynamic Registry. *J Am Coll Cardiol.* 2007;50:2029-36.

11. Marzocchi A, Saia F, Piovaccari G, Manari A, Aurier E, Benassi A, Cremonesi A, Percoco G, Varani E, Magnavacchi P, Guastaroba P, Grilli R, Maresta A. Long-term safety and efficacy of drug-eluting stents: two-year results of the REAL (REgistro AngiopLastiche dell'Emilia Romagna) multicenter registry. *Circulation.* 2007;115:3181-8.

12. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, Hopkins R, Tarride JE, Blackhouse G, Lazzam C, Cohen EA, Goeree R. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med.* 2007;357:1393-402.

13. Brodie BR, Stuckey T, Downey W, Humphrey A, Bradshaw B, Metzger C, Hermiller J, Krainin F, Juk S, Cheek B, Duffy P, Smith H, Edmunds J, Varanasi J, Simonton CA, Group S. Outcomes and Complications With Off-Label Use of Drug-Eluting Stents. Results From the STENT (Strategic Transcatheter Evaluation of New Therapies) Group. *J Am Coll Cardiol Interv.* 2008;1:405-14.

14. Galloe AM, Thuesen L, Kelbaek H, Thayssen P, Rasmussen K, Hansen PR, Bligaard N, Saunamaki K, Junker A, Aaroe J, Abildgaard U, Ravkilde J, Engstrom T, Jensen JS, Andersen HR, Botker HE, Galatius S, Kristensen SD, Madsen JK, Krusell LR, Abildstrom SZ, Stephansen GB, Lassen JF. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA.* 2008;299:409-16.

15. Win HK, Caldera AE, Maresh K, Lopez J, Rihal CS, Parikh MA, Granada JF, Marulkar S, Nassif D, Cohen DJ, Kleiman NS. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA.* 2007;297:2001-9.

16. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet.* 2007;369:667-78.

17. Honda Y, Fitzgerald PJ. Stent thrombosis: an issue revisited in a changing world. *Circulation.* 2003;108:2-5.

18. Rao SV, Shaw RE, Brindis RG, Klein LW, Weintraub WS, Peterson ED. On- versus off-label use of drug-eluting coronary stents in clinical practice (report from the American College of Cardiology National Cardiovascular Data Registry [NCDR]). *Am J Cardiol.* 2006;97:1478-81.

19. Beohar N, Davidson CJ, Kip KE, Goodreau L, Vlachos HA, Meyers SN, Benzuly KH, Flaherty JD, Ricciardi MJ, Bennett CL, Williams DO. Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA.* 2007;297:1992-2000.

20. Marroquin OC, Selzer F, Mulukutla SR, Williams DO, Vlachos HA, Wilensky RL, Tanguay JF, Holper EM, Abbott JD, Lee JS, Smith C, Anderson WD, Kelsey SF, Kip KE. A comparison of bare-metal and drug-eluting stents for off-label indications. *N Engl J Med.* 2008;358:342-52.

21. Jeremias A, Ruisi CP, Kirtane AJ, Lee T, Sylvia B, Pinto DS, Ho KK, Cutlip DE, Carrozza JP, Jr., Cohen DJ. Differential outcomes after sirolimus-eluting stent implantation: comparing on-label versus off-label patients in the 'real world'. *Coron Artery Dis.* 2008;19:111-5.

22. Shishehbor M, Goel S, Kapadia S, Bhatt D, Kelly P, Raymond R, Galla J, Brener S, Whitlow P, Ellis S. Long-term impact of drug-eluting stents versus bare-metal stents on all-cause mortality. *J Am Coll Cardiol.* 2008;52:1041-48.

23. Applegate RJ, Sacrinty MT, Kutcher MA, Santos RM, Gandhi SK, Baki TT, Little WC. "Off-label" stent therapy 2-year comparison of drug-eluting versus bare-metal stents. *J Am Coll Cardiol.* 2008;51:607-14.

24. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med.* 2008;358:331-41.

25. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW, SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961-72.

26. Brodie BR, Stuckey T, Downey W, Humphrey A, Nussbaum M, Laurent S, Bradshaw B, Metzger C, Hermiller J, Krainin F, Juk S, Cheek B, Duffy P, Simonton CA. Outcomes with drug-eluting stents versus bare metal stents in acute ST-elevation myocardial infarction: Results from the Strategic Transcatheter Evaluation of New Therapies (STENT) Group. *Catheter Cardiovasc Interv.* 2008;72:893-900.

27. Mauri L, Silbaugh TS, Garg P, Wolf RE, Zelevinsky K, Lovett A, Varma MR, Zhou Z, Normand SL. Drug-eluting or bare-metal stents for acute myocardial infarction. *N Engl J Med.* 2008;359:1330-42.

28. Kupferwasser LI, Amorn AM, Kapoor N, Lee MS, Kar S, Cercek B, Dohad S, Mirocha J, Forrester JS, Shah PK, Makkar RR. Comparison of drug-eluting stents with bare metal stents in unselected patients with acute myocardial infarction. *Catheter Cardiovasc Interv.* 2007;70:1-8.

29. Di Mario C, Morici N, Godino C, Goktekin O, Tamburino C, Barbagallo R, Antoniucci D, Grube E, Airoldi F, Zoccai GB, Colombo A, Sangiorgi GM. Predictors of restenosis after treatment of bifurcational lesions with paclitaxel eluting stents: a multicenter prospective registry of 150 consecutive patients. *Catheter Cardiovasc Interv.* 2007;69:416-24.

30. Werner GS, Krack A, Schwarz G, Prochnau D, Betge S, Figulla HR. Prevention of lesion recurrence in chronic total coronary occlusions by paclitaxel-eluting stents. *J Am Coll Cardiol.* 2004;44:2301-6.

31. Garcia-Garcia HM, Daemen J, Kukreja N, Tanimoto S, van Mieghem CA, van der Ent M, van Domburg RT, Serruys PW. Three-year clinical outcomes after coronary stenting of chronic total occlusion using sirolimus-eluting stents: insights from the rapamycin-eluting stent evaluated at Rotterdam cardiology hospital-(RESEARCH) registry. *Catheter Cardiovasc Interv.* 2007;70:635-9.

32. Mishkel GJ, Varghese JJ, Moore AL, Aguirre F, Markwell SJ, Shelton M. Short- and long-term clinical outcomes of coronary drug-eluting stent recipients presenting with chronic renal disease. *J Invasive Cardiol.* 2007;19:331-7.

33. Halkin A, Selzer F, Marroquin O, Laskey W, Detre K, Cohen H. Clinical outcomes following percutaneous coronary intervention with drug-eluting vs. bare-metal stents in dialysis patients. *J Invasive Cardiol.* 2006;18:577-83.

34. Bansal D, Muppidi R, Singla S, Sukhija R, Zarich S, Mehta JL, Sachdeva R. Percutaneous intervention on the saphenous vein bypass grafts--long-term outcomes. *Catheter Cardiovasc Interv.* 2008;71:58-61.

35. Chu WW, Rha SW, Kuchulakanti PK, Cheneau E, Torguson R, Pinnow E, Alexieva-Fournadjiev J, Pichard AD, Satler LF, Kent KM, Lindsay J, Waksman R. Efficacy of sirolimus-eluting stents compared with bare metal stents for saphenous vein graft intervention. *Am J Cardiol.* 2006;97:34-7.

36. Vermeersch P, Agostoni P, Verheye S, Van den Heuvel P, Convens C, Van den Branden F, Van Langenhove G. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol.* 2007;50:261-7.

37. Brilakis ES, Lichtenwalter C, de Lemos JA, Roesle M, Obel O, Haagen D, Saeed B, Gadiparthi C, Bissett JK, Sachdeva R, Voudris VV, Karyofillis P, Kar B, Rossen J, Fasseas P, Berger P, Banerjee S. A randomized-controlled trial of a paclitaxel-eluting stent vs. a similar bare metal stent in saphenous vein graft lesions. The SOS (Stenting of Saphenous Vein Grafts) Trial. *J Am Coll Cardiol.* 2009;53:919–28.

38. Elezi S, Dibra A, Mehilli J, Pache J, Wessely R, Schomig A, Kastrati A. Vessel size and outcome after coronary drug-eluting stent placement: results from a large cohort of patients treated with sirolimus- or paclitaxel-eluting stents. *J Am Coll Cardiol.* 2006;48:1304-9.

39. Zahn R, Hamm CW, Schneider S, Zeymer U, Richardt G, Kelm M, Levenson B, Bonzel T, Tebbe U, Sabin G, Nienaber CA, Senges J. Predictors of death or myocardial infarction during follow-up after coronary stenting with the sirolimus-eluting stent. Results from the prospective multicenter German Cypher Stent Registry. *Am Heart J.* 2006;152:1146-52.

40. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA.* 2007;297:159-68.

41. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA.* 2005;293:2126-30.

42. Daemen J, Tsuchida K, Stefanini GG, Vaina S, Kukreja N, De Jaegere PPT, Ong AT, van Domburg RT, Serruys PW. Two-year clinical follow-up of the unrestricted use of the paclitaxel-eluting stent compared to the sirolimus-eluting stent as part of the Taxus-stent evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. *EuroIntervention.* 2006;7:330-37.

43. Allocco DJ, Dawkins KD, Baim DS, Leon MB. The Impact of Non-Stent Related Progression of Underlying Coronary Artery Disease on Late Clinical Outcomes after Paclitaxel-Eluting Stents [TCT Abstract 346]. *Am. J. Cardiol.* 2008;102:137i-38i.

Appendix 1

ARRIVE programme clinical events committee members

David G. Hurrell, MD (Chairperson)
Director Nuclear Cardiology, Senior Consulting Cardiologist,
Minneapolis Heart Institute,
Minneapolis Cardiology Associations
Minneapolis, MN, USA

David D. Laxson, MD
Medical Director
Minnesota Heart Clinic
Edina, MN, USA

Yale L. Wang, MD
Cardiologist
Minneapolis Heart Institute,
Minneapolis Cardiology Association
Minneapolis, MN, USA

Robert F. Wilson, MD
Director, Interventional Cardiology
Cardiovascular Division, University of Minnesota
Minneapolis, MN, USA

Appendix 2

Cardiac event definitions in the ARRIVE programme

Cardiac event[a]	Definition
Cardiac death	Any death that cannot be attributed to a non-cardiac cause
Target vessel revascularisation[b]	Any attempted or successfully completed percutaneous or surgical revascularisation of a target vessel
Target lesion revascularisation[b,c]	Any TAXUS stent-related attempted or successfully completed percutaneous or surgical revascularisation of a target vessel
Myocardial infarction	One of the following criteria are met: • CK >2x upper limit of normal with a positive CK(MB) • CK >5x upper limit of normal with a positive CK(MB) for post-CABG cases • ECG evidence of new pathologic Q waves (lasting 0.04 seconds or more) in 2 contiguous leads with positive CK(MB)
Major cardiac events	Composite of cardiac death, myocardial infarction, and target vessel revascularisation
Stent thrombosis	Academic Research Consortium definitions definite/probable[d]

[a] All cardiac events were adjudicated by a Clinical Events Committee (Appendix 1). Cardiac enzyme and electrocardiographic data pre- and post-stent implantation were collected per local practice. Follow-up was carried out via clinic visit or telephone contact with a study research nurse; data were recorded on structured case report forms. [b] Patients experiencing a revascularisation within 2-years based on clinical necessity as per operator practice received additional post-revascularisation follow-up through 12 months. [c] An event was considered "TAXUS-stent-related" if it occurred at the stented segment or if the relationship to the TAXUS stent could not be excluded based upon available information. [d] Cutlip DE, et al.[7] CK: creatine kinase; CABG: coronary artery bypass graft; ECG: electrocardiogram

Appendix 3

Baseline characteristic variables used in predictor modelling

Acute MI	IVUS post deployment	PCI, previous
Age>70	IVUS pre-deployment	Postprocedure dilatation
Bifurcation	LAD as target vessel	Preprocedure dilatation
Brachytherapy, prior	Left main disease	Preprocedure TIMI=0
CABG, previous	Left main stenting	Renal disease[a]
Cardiogenic shock	Lesion >28 mm	RVD <3 mm
Chronic total occlusion	Lesion calcification[c]	Smoking at baseline
Congestive heart failure[b]	Lesion type B2/C	Stent inflation pressure >14 atm
Diabetes, insulin treated	MI, previous	Stroke, previous
Diabetes, not requiring insulin	Multiple overlapping stents	Thienopyridine <12 months
Gender, male	Multiple stents per lesion	Thienopyridine <6 months
Hypercholesterolaemia[d]	Multivessel disease	Tortuosity, severe
Hypertension[d]	Multivessel stenting	Vein graft
In-stent restenosis	Ostial lesion	

Hazard ratios were assessed with the Cox proportional hazards regression model; backward selection was used; the threshold to stay in the model was set at 0.10. [a] Site reported as serum creatinine >3.0 mg/dL or patient on dialysis [b] Site reported as NYHA Class ≥III [c] Moderate and severe [d] Patient was reported as having this condition and may or may not have been receiving medication for it. CABG: coronary artery bypass graft; IVUS: intravascular ultrasound; LAD: left anterior descending artery; MI: myocardial infarction; PCI: percutaneous coronary intervention; RVD: reference vessel diameter; TIMI: thrombolysis in myocardial infarction

Appendix 4

Investigators and institutions participating in the ARRIVE programme

Investigator[a]	Institution
	ARRIVE 1
Lasala J, study PI	Washington University School of Medicine, St. Louis, MO
Cox D, study Co-PI	Mid-Carolina Cardiology Presbyterian Hospital, Charlotte, NC
Ali N	Clear Lake Regional Medical Center, Webster, TX
Armstrong B	Cardiovascular Associates, PC, Kingsport, TN
Baucum J	Greenville Hospital Systems, Greenville, SC
Carney R	Trinity Mother Frances Hospital, Tyler, TX
Chambers J	Metro Cardiology Consultants, Coon Rapids, MN
Chhabra A	Willis Knighton, Shreveport, LA
Cohen B	Morristown Memorial, Morristown, PA
Cohen M	Abington Memorial Hospital, Abington, PA
Dobies D	Genesys Regional Medical Center, Grand Blanc, MI
Grady T	Care Foundation, Wausau, WI
Greenberg J	Florida Heart Institute, Orlando, FL
Hearne S	Delmarva Heart Research Foundation, Inc., Salisbury. MD
Hill R	Cardiology Associates of NEA, Jonesboro, AR
Hockstad E	Research Medical Center, Kansas City, MO
Isaacson T	Heart Hospital of South Dakota, Sioux Falls, SD
Jenkins G	Methodist Dallas Medical Center, Dallas, TX
Johnson S	Alexian Brothers Medical Center, Elk Grove, IL
Katopodis J	Tallahassee Memorial Hospital, Tallahassee, FL
Kellett M	Maine Medical Center, Portland, ME
Kiernan F	Hartford Hospital, Hartford, CT
Kuehl W	Asheville Cardiology Associates, PA, Asheville, NC
Lee A	Good Samaritan, San Jose, CA
Leggett J	Overlake Hospital, Bellevue, WA
Low R	University of California Davis Medical Center, Sacramento, CA
Mann T	Wake Medical Center, Raleigh, NC
Meyer T	Georgia Heart and Vascular, Macon, GA
Miller M	Pitt County Memorial Hospital, Greenville, NC
Miller W	Poudre Valley Hospital, Fort Collins, CO
Muhlestein B	LDS Hospital, Salt Lake City, UT
Nukta E	Cleveland Cardiovascular Research Foundation, Fairview Park, OH
Orlow S	Lutheran Hospital/NIRA, Fort Wayne, IN
Overlie P	Texas Cardiac Center, Lubbock, TX
Patel J	Cardiovascular Consultants of Nevada, Las Vegas, NV
Paulowski J	Aultman Hospital, Canton, OH
Rabinowitz A	South Texas Cardiovascular Consultants, San Antonio, TX
Raybuck B	INOVA Fairfax Hospital, Falls Church, VA
Revtyak G	St. Francis Hospital, Beech Grove, IN
Robken J	Genesis Medical Center, Davenport, LA
Seigel R	Advanced Cardiac Specialists, Gilbert, AZ
Studeny M	St. Mary's Hospital, Huntington, WV
Untereker W	Presbyterian University of Pennsylvania Medical Center, Philadelphia, PA
Valentino V	Our Lady of Lourdes, Lafayette, LA
Ver Lee P	Eastern Maine Medical Center, Bangor, ME
Villa A	Palm Beach Gardens Medical Center, Palm Beach Gardens, FL
Wehrli C	St. Peters Hospital, Olympia, WA
Weiss M	Westchester County Medical Center, Valhalla, NY
Wyman R	Little Company of Mary Hospital, Torrance, CA
Zetterlund P	Salinas Valley Memorial Hospital, Salinas, CA

Investigator[a]	Institution
	ARRIVE 2
Lasala J, study PI	Washington University School of Medicine, St. Louis, MO
Cox D, study Co-PI	Mid-Carolina Cardiology Presbyterian Hospital, Charlotte, NC
Bach M	Jersey Shore University Medical Center, Neptune, NJ
Bachinsky WB	Pinnacle Health/Moffitt Heart & Vascular, Harrisburg, PA
Baran KW	St. Paul Heart Clinic, St. Paul, MN
Battista SC	Minnesota Heart Clinic/ Fairview Southdale Hospital, Edina, MN
D'Haem C	Thoracic & Cardiovascular Healthcare Foundation, Lansing, MI
Breall JA	Krannert Institute of Cardiology, Indianapolis, IN
Coppola JT	Saint Vincent's Catholic Medical Center of New York, New York, NY
Corey WH	Indiana Heart Hospital, Indianapolis, IN
Croft CH	Health First Clinical Research Institute, Melbourne, FL
Davakis NJ	Cardiovascular Research Institute, Inc., Columbus, OH
Del Core MG	The Creighton Cardiac Center, Omaha, NE
Federici RE	New Mexico Heart Institute, Albuquerque, NM
Foster MT	Baptist Hospital of East Tennessee, Knoxville, TN
Gandhi AN	Cardiology Associates of Northwest Indiana, Munster, IN
Garas SM	Saint Vincent's Medical Center, Jacksonville, FL
Goodwin MJ	Midwest Heart Foundation, Lombard, IL
Haas, RC	Heart Center of Tulsa, Tulsa, OK
Horwitz PA	University of Iowa Hospital, Iowa City, IA
Jenny DB	Cardiology Associates of Green Bay, Green Bay, WI
Kabour A	St. Vincent Mercy Medical Center, Toledo, OH
Kandzari D/Rao S	Duke University Medical Center, Durham, NC
Khanna PK	Desert Cardiology Center, Rancho Mirage, CA
Koren PA	Cardiovascular Associates of Delaware Valley, Haddon Heights, NJ
Lee CD	Idaho Cardiology Associates, Boise, ID
Lee TC	Bakersfield Memorial Hospital, Bakersfield, CA
Lewis DH	South Central Wisconsin Heart, Madison, WI
Lewis S J	Bethesda North Hospital/ Hatton Institute, Cincinnati, OH
Lombardi WL	North Cascade Cardiology, PLLC, Bellingham, WA
Lundstrom RJ	Kaiser Permanente Medical Center, San Francisco, CA
Mahoney PD	Sentara Norfolk General Hospital, Norfolk, VA
Malik AZ	Heart Center of North Texas, Fort Worth, TX
Martin JL	Main Line Health Heart Center, Radnor, PA
Morris DL	Albert Einstein Medical Center, Philadelphia, PA
Myers PR	St. Thomas Hospital, Nashville, TN
Nielsen CD	Medical University of South Carolina, Charleston, SC
Pasquini JA	Mid Carolina Cardiology / Presbyterian Hosp., Charlotte, NC
Pow TK	Great Lakes Heart & Vascular Institute PC, St. Joseph, MI
Quintana OE	McAllen Heart Clinic, McAllen, TX
Rees AP	Cardiovascular Research Foundation of Louisiana, Baton Rouge, LA
Rizik DG	Scottsdale Healthcare, Scottsdale, AZ
Rogers EW	Cardiology Consultants, Pensacola, FL
Rosenthal AD	The Heart and Vascular Institute of Florida, St. Petersburg, FL
Schweiger MJ	Baystate Medical Center, Springfield, MA
Shaw D	Christus St. Frances Cabrini Hospital, Alexandria, LA
Singh J	Barnes/Jewish Hospital, St. Louis, MO
Srinivasan V	Western Pennsylvania Hospital, Pittsburgh, PA
Stella JF	Heart Care Research Foundation, Merrionette Park , IL
Tadros PN	University of Kansas Hospital, Kansas City, KS
Tannenbaum MA	Iowa Heart Center Research, Des Moine, IA
Uretsky B/Lui C	University of Texas Medical Branch, Galveston, TX
Weiner BH	St. Vincent Hospital at Worcester Medical Center, Worcester, MA
Wiet SP	Advocate Christ Medical Center, Oak Lawn, IL
Zirafi CM	Parma Community General Hospital, Parma, OH

[a] Site principal investigators are listed; Co-PI: Co-Principal Investigator