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ORIGINAL RESEARCH

Utility of the ACC/AHA Lesion Classification to Predict Outcomes After Contemporary DES Treatment: Individual Patient Data Pooled Analysis From 7 Randomized Trials

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BACKGROUND: Use of the modified American College of Cardiology (ACC)/American Heart Association (AHA) lesion classification as a prognostic tool to predict short- and long-term clinical outcomes after percutaneous coronary intervention in the modern drug-eluting stent era is uncertain.

METHODS AND RESULTS: Patient-level data from 7 prospective, randomized trials were pooled. Clinical outcomes of patients undergoing single lesion percutaneous coronary intervention with second-generation drug-eluting stent were analyzed according to modified ACC/AHA lesion class. The primary end point was target lesion failure (TLF: composite of cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization). Clinical outcomes to 5 years were compared between patients treated for noncomplex (class A/B1) versus complex (class B2/C) lesions. Eight thousand five hundred sixteen patients (age 63.1±10.8 years, 70.5% male) were analyzed. Lesions were classified as A, B1, B2, and C in 7.9%, 28.5%, 33.7%, and 30.0% of cases, respectively. Target lesion failure was higher in patients undergoing percutaneous coronary intervention of complex versus noncomplex lesions at 30 days (2.0% versus 1.1%, *P*=0.004), at 1 year (4.6% versus 3.0%, *P*=0.0005), and at 5 years (12.4% versus 9.2%, *P*=0.0001). By multivariable analysis, treatment of ACC/AHA class B2/C lesions was significantly associated with higher rate of 5-year target lesion failure (adjusted hazard ratio, 1.39 [95% CI, 1.17–1.64], *P*=0.0001) driven by significantly higher rates of target vessel myocardial infarction and ischemia-driven target lesion revascularization.

CONCLUSIONS: In this pooled large-scale analysis, treating complex compared with noncomplex lesions according to the modified ACC/AHA classification with second-generation drug-eluting stent was associated with worse 5-year clinical outcomes. This historical classification system may be useful in the contemporary era for predicting early and late outcomes following percutaneous coronary intervention.

Key Words: drug-eluting stents ■ percutaneous coronary intervention ■ target lesion failure

The American College of Cardiology/American Heart Association (ACC/AHA) lesion morphology classification[1] and the subsequent modified ACC/AHA classification[2] were developed in the late 1980s to identify patients and lesions most suitable for percutaneous coronary intervention (PCI) and to predict procedural success. According to the modified classification, lesions are classified into 3 groups (A, B, and C) based on 11 angiographic characteristics, with the intermediate risk group B further divided

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CLINICAL PERSPECTIVE

What Is New?

- Target lesion failure rates were higher in patients treated for complex compared with noncomplex lesions.
- These differences were driven by higher rates of target vessel myocardial infarction and ischemia-driven target lesion revascularization.
- Treatment of American College of Cardiology/American Heart Association class B2/C lesions was independently associated with target lesion failure (adjusted hazard ratio, 1.39 [95% CI, 1.17–1.64], *P*=0.0001).

What Are the Clinical Implications?

- In the present large-scale individual patient data pooled analysis, treatment of complex coronary artery lesions according to the modified American College of Cardiology/American Heart Association classification with second-generation drug-eluting stents was associated with worse clinical outcomes up to 5 years compared with the treatment of noncomplex lesions.
- Therefore, the historical American College of Cardiology/American Heart Association lesion classification still has present-day relevance and utility for predicting early and late outcomes following percutaneous coronary intervention with contemporary drug-eluting stents.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
DES	drug-eluting stents
ID-TLR	ischemia-driven target lesion revascularization
TIMI	thromoblysis in myocardial infarction
TLF	target lesion failure
TV-MI	target vessel myocardial infarction
TVR	target vessel revascularization

into class B1 and B2 according to the presence of 1 or 2 adverse characteristics.[2] A binary classification is commonly used, with class A and B1 lesions categorized as "noncomplex" and class B2 and C lesions categorized as "complex."

The current utility of this classification system, which was validated during the early balloon angioplasty era,[2,3] has been questioned, especially after stent implantation.[4–6] Few studies have examined its role in the contemporary PCI era, and those have reported conflicting data.[7–9] We therefore sought to evaluate the impact of lesion complexity according to the modified ACC/AHA classification on short- and long-term clinical outcomes after contemporary drug-eluting stent (DES) implantation from a large patient-level pooled database of randomized clinical trials.

METHODS

We combined data from 7 prospective, randomized trials enrolling patients with second-generation DES that were maintained at the Cardiovascular Research Foundation (New York, NY) in which treated lesion ACC/AHA class was determined at an angiographic core laboratory. The data that support the findings of this study are available from the corresponding author upon reasonable request. Clinical follow-up was performed for up to 5 years. The designs of the trials have been previously described and are summarized in Supplemental Table S1.[10–16] As we sought to study contemporary DES outcomes, only patients in which a single lesion was treated with a contemporary second-generation DES (Xience V or Xience Prime, Abbott Vascular, Santa Clara, CA; Promus, Boston Scientific, Marlborough, MA; Nobori, Terumo, Tokyo, Japan; and Resolute Integrity, Medtronic, Santa Rosa, CA) were included in the analysis. Patients were censored at time of first event or at last follow-up time, whichever occurred first. Each trial was approved by the institutional review board or ethics committee at the respective participating centers, and all patients signed written informed consent before randomization.

ACC/AHA Lesion Morphology Classification

Treated lesions were classified according to modified ACC/AHA classification criteria (Figure)[1,2] by the angiographic core laboratory as either A, B1, B2, or C based on the independent angiographic core laboratory assessment performed for each study.

Endpoints and Definitions

The primary endpoint of interest was the rate of target lesion failure (TLF) defined as the composite of cardiac death, target vessel myocardial infarction (TV-MI), or ischemia-driven target lesion revascularization. Secondary end points included rates of (1) major adverse cardiac events, defined as the composite of cardiac death, any MI, or ischemia-driven target lesion revascularization; and (2) target vessel failure, defined as the composite of cardiac death, TV-MI, or ischemia-driven target vessel revascularization. Definite and probable stent thromboses were defined according to the Academic Research Consortium.[17] Events as

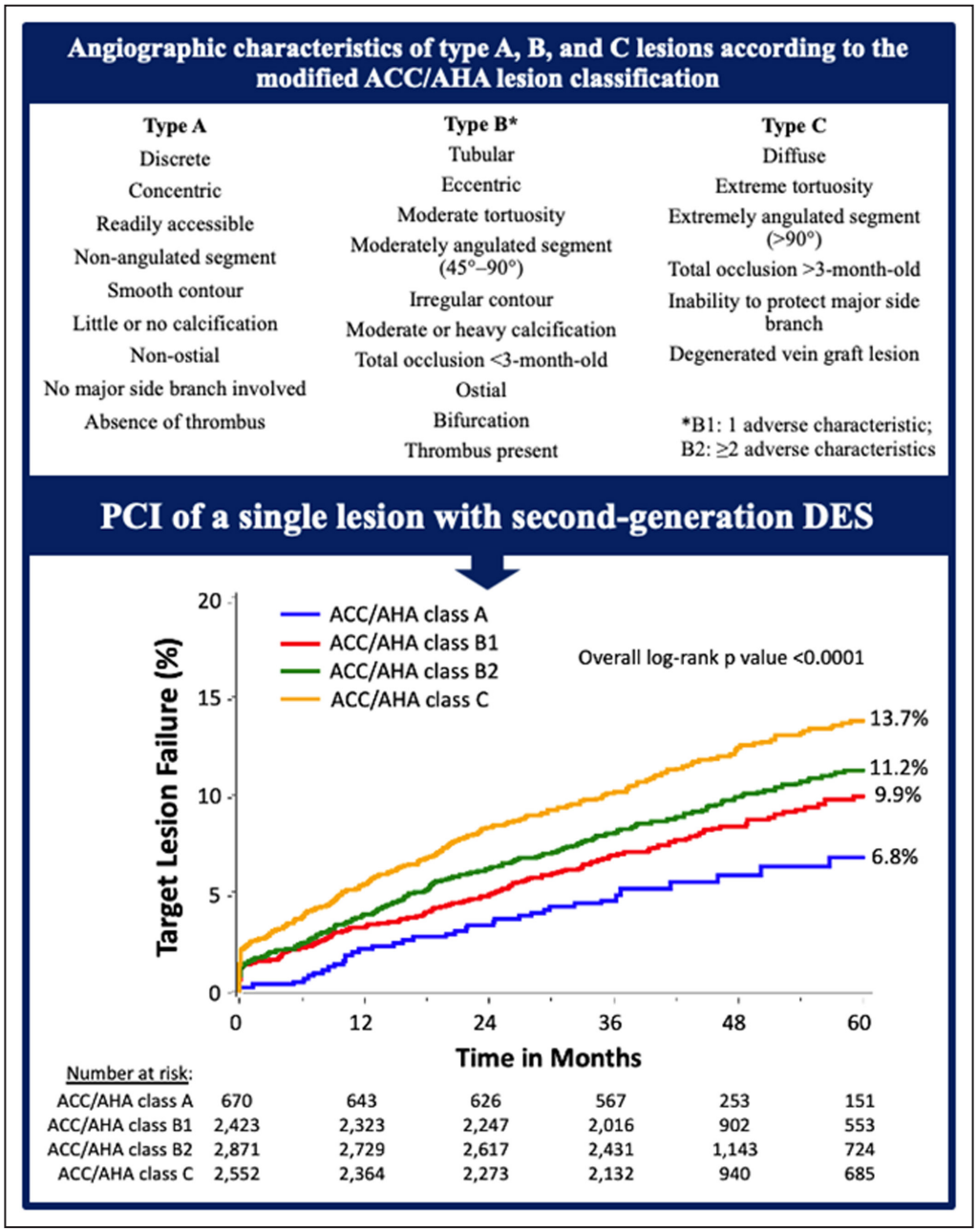

Figure. Angiographic characteristics of ACC/AHA class type A, B, and C and corresponding 5-year rates of target lesion failure.
ACC indicates American College of Cardiology; AHA, American Heart Association; DES, drug-eluting stent; and PCI, percutaneous coronary intervention.

independently adjudicated in each trial were used for the pooled analysis. All end points were evaluated at 30 days, 1 year, and 5 years after treatment.

Statistical Analysis

Continuous data are presented as mean±SD and were compared with the Student *t*-test and ANOVA for 2-group and 4-group comparisons, respectively. Categorical data are presented as percentage and counts, and differences were assessed with the χ^2 test. Primary and secondary endpoints were analyzed in terms of time-to-first event; rates are presented using Kaplan–Meier estimates as percentages with number of events, with differences assessed using the log-rank test. The significantly associated predictors of time to first event were determined by multivariable Cox proportional hazard regression, adjusted for study and age, male sex, diabetes, hypertension, hyperlipidemia, prior coronary artery bypass grafting, prior MI, prior PCI, body mass index, acute coronary syndrome

presentation, and complex versus noncomplex ACC/AHA lesion classification. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population and Lesion Characteristics

A total of 8516 patients (age 63.1±10.8 years, 70.5% male) with a single stented lesion were included in the pooled analysis; the median follow-up was 1106 days (Q1: 1091, Q3: 1800). Lesions were classified as A, B1, B2, and C in 670 (7.9%), 2423 (28.5%), 2871 (33.7%), and 2552 (30.0%) of cases, respectively. Thus, 3093 lesions (36.3%) were categorized as noncomplex (class A or B1) while 5423 lesions (63.7%) were categorized as complex (class B2 or C). Clinical, procedural, and angiographic characteristics of the study population according to ACC/AHA class are presented in Table 1. Complex lesions (class B2/C) were more frequently located in the right coronary artery and were longer, had smaller minimal lumen diameter, and had more severe calcification and vessel tortuosity.

Clinical Outcomes

At 30 days, TLF was higher among patients undergoing PCI in complex lesions compared with noncomplex lesions (2.0% versus 1.1%, hazard ratio [HR], 1.9 [95% CI, 1.22–2.96], *P*=0.004), a difference driven by higher rates of TV-MI (Table S2). There was no difference in the 30-day rate of stent thrombosis in patients with complex and noncomplex lesions (0.3% versus 0.2%; HR, 1.56 [95% CI, 0.62–3.96], *P*=0.25).

As shown in the Figure, 5-year TLF rates progressively increased with ACC/AHA lesion class. Detailed 1-year and 5-year clinical outcomes are shown in Table 2 and Table S3. At both 1 and 5 years, TLF rates were higher in patients treated for complex compared with noncomplex lesions. These differences were driven by significantly higher rates of TV-MI, and ischemia-driven target lesion revascularization. Stent thrombosis rates were also higher in complex compared with noncomplex lesions at 5 years. The rate of late stent thrombosis (occurring between 30 days and 1 year) was similar between groups (0.2% and 0.1%, *P*=0.11), whereas very late stent thrombosis (between 1 and 5 years) was more frequent after treatment of complex lesions (1.2% versus 0.4%, *P*=0.005).

Multivariable Analysis

Predictors of TLF at 5 years are shown in Table S4. Treatment of ACC/AHA class B2/C lesions was independently associated with TLF (adjusted HR, 1.39 [95% CI, 1.17–1.64], *P*=0.0001). Other significantly associated predictors of 5-year TLF were age, diabetes mellitus, and prior coronary artery bypass grafting.

DISCUSSION

In this large-scale individual patient data pooled analysis from 7 randomized trials, we investigated the impact of lesion complexity, according to the modified ACC/AHA classification, on short- and long-term clinical outcomes of patients undergoing PCI with implantation of second generation DES. The main findings of the present analysis are as follows: (1) the rate of TLF increased in proportion to lesion complexity at all time points; (2) patients who underwent PCI for complex lesions (type B2 or C) experienced higher rates of TLF compared with patients who underwent PCI for noncomplex lesions, driven by higher rates of TV-MI and ischemia-driven target lesion revascularization; (3) long-term stent thrombosis rates were also increased in complex lesions, despite use of second-generation DES; and (4) by multivariable analysis, ACC class B2/C was independently associated with an increased rate of TLF at 5 years.

The ACC/AHA lesion classification was originally established 3 decades ago to identify patients suitable for balloon angioplasty and to predict lesion success. The anticipated success rates of balloon angioplasty at that time were >85%, 60% to 85%, and <65% for lesion types A, B, and C, respectively,[1] emphasizing the utility of this risk instrument to inform interventionalist cardiologists as to whether specific lesions should be treated.

Considering the marked advancements in PCI technologies and techniques since the early angioplasty era, and the very high procedural success rates across all lesion types reported in current studies,[18–20] the utility of the ACC/AHA classification in the current era has been questioned. While the utility of this classification to predict procedural success during the early angioplasty era was validated,[2,3] doubts regarding the usefulness of this classification after the introduction of coronary stents were raised.[4–6] Nonetheless, despite its uncertain role, the modified ACC/AHA classification continues to be used in clinical research and practice.

Alfonso et al.[7] reported superior acute and long-term angiographic outcome in patients undergoing PCI of noncomplex lesions (classes A/B1) compared with complex lesions (classes B2/C). A subanalysis from the Acute Catheterization and Urgent Intervention Triage strategy trial demonstrated an increased rate of short-term events in patients with acute coronary syndromes undergoing PCI of type C lesions.[8] Recently, Theuerle et al.[9] evaluated the outcomes of 13 701 patients undergoing PCI between 2005 and 2013. In this study, ACC/AHA classification remained a strong predictor of procedural success, and increasing lesion complexity

Table 1. Clinical, Angiographic, and Procedural Characteristics of the Study Population According to Noncomplex Versus Complex ACC/AHA Lesion Class

Clinical, procedural and angiographic data	Noncomplex—Class A/B1 (N=3093)	Complex—Class B2/C (N=5423)	*P* value
Clinical data			
Age, y	62.5±10.8	63.5±10.8	<0.0001
Male sex	69.0% (2133/3093)	71.3% (3868/5423)	0.02
Diabetes	24.0% (743/3092)	23.0% (1249/5422)	0.30
Insulin-treated	7.0% (215/3092)	6.7% (363/5422)	0.65
Current smoker (≤30 d)	25.7% (785/3060)	25.5% (1371/5376)	0.88
Hypertension	65.7% (2031/3092)	61.0% (3306/5420)	<0.0001
Hyperlipidemia	64.6% (1978/3064)	61.8% (3327/5385)	0.01
Body mass index, kg/m^2	29.2±5.6	28.7±5.2	<0.0001
Prior coronary artery bypass grafting	6.1% (190/3091)	8.0% (433/5421)	0.002
Prior PCI	20.3% (627/3082)	19.2% (1034/5398)	0.18
Prior myocardial infarction	20.8% (636/3051)	21.3% (1143/5371)	0.64
LVEF <40%	3.7% (17/462)	5.2% (43/832)	0.22
Acute coronary syndrome	42.1% (1216/2886)	48.1% (2501/5196)	<0.0001
STEMI	6.8% (209/3093)	13.6% (737/5423)	<0.0001
NSTEMI	12.4% (382/3093)	14.6% (794/5423)	0.003
Unstable angina	21.7% (625/2886)	18.7% (970/5196)	0.001
Stable coronary artery disease	57.9% (1670/2886)	51.9% (2695/5196)	<0.0001
Type of stent			
Zotarolimus-eluting	10.2% (316/3093)	14.2% (772/5423)	<0.0001
Everolimus-eluting	75.6% (2338/3093)	69.3% (3760/5423)	<0.0001
Biolimus-eluting	14.2% (439/3093)	16.4% (891/5423)	0.006
Pre-PCI angiography (core lab)			
Reference vessel diameter, mm	2.76±0.82	2.79±0.70	0.04
Minimal lumen diameter, mm	0.82±0.40	0.78±0.45	<0.0001
Diameter stenosis, %	72.2±14.9	75.1±16.6	<0.0001
Lesion length, mm	11.6±5.4	19.4±11.1	<0.0001
Lesion location			
Left anterior descending artery	44.1% (1365/3093)	45.6% (2471/5423)	0.20
Right coronary artery	28.4% (879/3093)	34.7% (1884/5423)	<0.0001
Left circumflex	27.2% (840/3093)	21.1% (1142/5423)	<0.0001
Left main	0.3% (10/3093)	1.4% (75/5423)	<0.0001
Calcification (moderate/severe)	9.3% (266/2857)	40.8% (1957/4802)	<0.0001
Tortuosity (moderate/severe)	1.7% (8/472)	10.3% (89/860)	<0.0001
TIMI flow 0–1	4.4% (135/3093)	18.2% (987/5423)	<0.0001
Total stent length implanted, mm	18.7±7.5	32.2±21.2	<0.0001
Post-PCI angiography (core lab)			
TIMI flow			
0 or 1	0.03% (1/3091)	0.3% (14/5414)	0.02
2	0.7% (22/3091)	1.1% (62/5414)	0.052
3	99.3% (3068/3091)	98.7% (5343/5414)	0.02
Minimal lumen diameter, mm	2.43 (1.37)	2.43 (1.00)	0.96
Diameter stenosis, %	12.2±9.0	13.6±10.2	<0.0001

Values are mean±SD or % (n/N). ACC indicates American College of Cardiology; AHA, American Heart Association; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

Table 2. Clinical Outcomes According to Lesion Complexity

Outcomes	Noncomplex—Class A/B1 (N=3093)	Complex—Class B2/C (N=5423)	Adjusted HR (95% CI)*	*P* value*
1 y				
Target lesion failure†	3.0% (92)	4.6% (249)	1.60 (1.23–2.09)	0.0005
Major adverse cardiac events‡	3.1% (95)	4.7% (255)	1.59 (1.23–2.07)	0.0005
Target vessel failure§	3.8% (118)	5.5% (295)	1.49 (1.18–1.89)	0.0009
Death	1.1% (34)	1.7% (90)	1.25 (0.82–1.90)	0.30
Cardiac*	0.5% (16)	1.0% (53)	1.70 (0.97–2.99)	0.07
Noncardiac*	0.6% (18)	0.7% (37)	1.11 (0.62–1.96)	0.73
Myocardial infarction	1.4% (44)	2.3% (124)	1.64 (1.12–2.40)	0.01
Target vessel	1.3% (41)	2.2% (117)	1.66 (1.13–2.45)	0.01
Any revascularization	5.0% (129)	5.2% (237)	1.25 (0.98–1.60)	0.07
Target lesion (ischemia-driven)	1.4% (44)	2.1% (114)	1.70 (1.15–2.51)	0.008
Target vessel (ischemia-driven)	2.4% (73)	3.0% (163)	1.42 (1.05–1.93)	0.02
Nontarget vessel	2.9% (76)	2.6% (118)	1.15 (0.83–1.60)	0.39
Stent thrombosis*	0.3% (8)	0.6% (30)	1.97 (0.90–4.31)	0.09
Definite*	0.3% (8)	0.4% (23)	1.52 (0.68–3.43)	0.31
Probable*	0.0% (0)	0.1% (7)	…	…
5 y				
Target lesion failure†	9.2% (229)	12.4% (561)	1.39 (1.17–1.64)	0.0001
Major adverse cardiac events‡	9.8% (247)	13.4% (601)	1.38 (1.17–1.62)	0.0001
Target vessel failure§	12.6% (309)	14.8% (669)	1.26 (1.09–1.46)	0.002
Death	7.4% (158)	8.2% (330)	1.00 (0.82–1.23)	0.98
Cardiac	2.9% (62)	3.8% (161)	1.18 (0.86–1.63)	0.30
Noncardiac	4.7% (96)	4.6% (169)	0.89 (0.68–1.16)	0.37
Myocardial infarction	3.2% (84)	5.2% (241)	1.71 (1.30–2.25)	0.0001
Target vessel	2.4% (65)	4.1% (197)	1.84 (1.35–2.50)	0.0001
Any revascularization	15.3% (323)	16.6% (585)	1.19 (1.02–1.39)	0.02
Target lesion (ischemia-driven)	5.3% (133)	7.0% (299)	1.38 (1.10–1.73)	0.005
Target vessel (ischemia-driven)	9.2% (222)	10.0% (432)	1.20 (1.01–1.43)	0.04
Nontarget vessel	9.6% (190)	9.1% (309)	1.16 (0.95–1.42)	0.15
Stent thrombosis	0.7% (18)	1.8% (72)	2.13 (1.23–3.70)	0.007
Definite*	0.5% (15)	1.3% (55)	1.91 (1.07–3.41)	0.03
Probable*	0.2% (3)	0.5% (17)	2.44 (0.71–8.39)	0.16

HR indicates hazard ratio.
*Denotes there were too few events to adjust the HR, and thus a univariate HR is presented.
†Defined as the composite of cardiac death, ischemia-driven target lesion revascularization, and target vessel-myocardial infarction.
‡Defined as the composite of cardiac death, ischemia-driven target lesion revascularization, and any myocardial infarction.
§Defined as the composite of cardiac death, target vessel-myocardial infarction, and ischemia-driven target vessel revascularization.

correlated with higher rates of mortality and major adverse cardiac events at both 30 days and 12 months.

The present analysis differed from these prior studies in several important aspects. First, we included a large number of patients, all enrolled in randomized controlled trials with independent angiographic core laboratory determination of ACC/AHA class and event adjudication. Second, all patients included in our analysis underwent implantation of second generation DES. Third, we assessed the impact of lesion complexity on long-term outcomes (up to 5 years). We found that, despite treatment with second-generation DES, complex lesions as defined by the modified ACC/AHA criteria correlated with increased rates of stent failure (TLF) at all time points from 30 days through 5 years driven by increased rates of TV-MI, and ischemia-driven target lesion revascularization as well as stent thrombosis.

The reasons for the unfavorable long-term outcomes of patients treated for complex lesions were unclear. It has been proposed that lesion complexity may be a marker of more advanced atherosclerosis.[9] In the present study, patients with complex lesions were more likely to have a history of previous MI and coronary artery bypass grafting. However, adverse events were most frequently target lesion–related; the rates of nontarget lesion revascularizations were not

increased after PCI of complex lesions. In this regard, postprocedural angiographic parameters including the percent diameter stenosis were better after treatment of noncomplex lesions than complex lesions; this is not surprising given the greater baseline diameter stenosis, longer lesion length, and the increased prevalence of calcification, tortuosity, and reduced thrombolysis in myocardial infarction (TIMI) flow in complex lesions. Thus, even use of modern DES was not sufficient to overcome the challenges presented by complex ACC/AHA class B2 and C lesions. Further studies are warranted to determine whether the differences in outcomes between noncomplex and complex lesions may be further narrowed by greater use of lesion preparation (e.g., atherectomy or lithotripsy),[21,22] routine use of intravascular imaging,[23,24] and other advanced dedicated techniques for bifurcation lesions, chronic total occlusions, thrombus, etc.[25]

While clinical treatment decisions are likely to be informed from the knowledge of outcomes in individual lesion characteristics (such as bifurcations, severe calcification, etc.), given the results from the present study lesion dichotomization according to the ACC/AHA classification may be useful in summary statistics to risk stratify outcomes or as a summary covariate in parsimonious multivariable models to avoid variable collinearity or model overfitting.

Other classification systems to predict procedural success have been evaluated previously. For example, based on the relationship between baseline vessel patency and procedural success rates, the Society of Coronary Angiography and Interventions classification system recognizes 4 groups according to ACC/AHA class C versus non-C and whether the lesion is patent.[26] Other scores have also included clinical variables. The Mayo Clinic procedural complications risk score[27] includes 8 clinical and angiographic variables (age, cardiogenic shock, serum creatinine level, urgent or emergent procedure, NYHA functional class III or IV heart failure, thrombus, and left main or multivessel disease). Compared with the ACC/AHA classification system, this score was reported to have superior discrimination to predict cardiovascular complications but inferior discrimination for angiographic success.[28] Further studies are warranted to determine the optimal prediction models for early procedural success and late outcomes in the contemporary DES era.

A strength of the present study is that the analyses were derived from an individual patient data pooled database derived from 7 randomized trials enrolling a diverse group of patients from numerous geographies, affording examination of temporal outcomes and multivariable analysis. However, several limitations should be considered. First, minor variations in the definitions of the components of TLF between studies may have introduced some imprecision. Second, interstudy variations in inclusion/exclusion criteria, duration of follow-up, type of stents, and other technologies used may have introduced heterogeneity and influenced the outcomes. In this regard, detailed data on use of intravascular imaging, physiologic lesion assessment, and lesion preparation strategies were not available for all studies. Third, our study included only patients enrolled in randomized trials. In some of these studies, certain complex lesions and strategies (eg, chronic total occlusions, planned 2-stent bifurcations, etc.) were excluded. Fourth, to avoid clustering effects and isolate the impact of lesion complexity, we excluded from the analysis patients who had >1 lesion treated. However, we performed the same analysis on the entire population enrolled in the same studies and the results were similar (data not shown). Finally, a detailed analysis of each angiographic morphologic characteristic that comprises complex lesions was beyond the scope of the present report. Further studies are required to determine which lesion characteristics are most strongly associated with early and late adverse outcomes.

CONCLUSIONS

In the present large-scale individual patient data pooled analysis, treatment of complex coronary artery lesions according to the modified ACC/AHA classification with second-generation DES was associated with worse clinical outcomes up to 5 years compared with treatment of noncomplex lesions. The historical ACC/AHA lesion classification thus still has present-day relevance and utility for the prediction of early and late outcomes following PCI with contemporary DES.

ARTICLE INFORMATION

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Supplemental Material

Table S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Description of the Prospective Randomized Trials Used in the Pooled Analysis.

Study	Year	Second-generation drug-eluting stent	Number of patients included in the pooled analysis	Endpoint	
				Clinical endpoint	Timepoint
COMPARE[10]	2010	EES (XIENCE)	6.9% (589/8516)	Death, myocardial infarction, target vessel revascularization	1 year
COMPARE II[11]	2013	BES (Nobori), EES (XIENCE/Promus)	23.4% (1991/8516)	Cardiac death, myocardial infarction, target vessel failure	1 year
PLATINUM[14]	2011	EES (Promus)	15.6% (1332/8516)	Target lesion failure	1 year
SPIRIT III[12]	2008	EES (XIENCE)	6.6% (559/8516)	In-segment late lumen loss	9 months
SPIRIT IV[13]	2010	EES (XIENCE)	21.5% (1835/8516)	Target lesion failure	1 year
TWENTE[15]	2012	ZES (Resolute), EES (XIENCE)	10.1% (857/8516)	Target vessel failure	1 year
TWENTE II[16]	2014	ZES (Resolute), EES (Promus)	15.9% (1353/8516)	Target lesion failure	1 year

Values are % (n/N). BES = biolimus-eluting stent; EES = everolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table S2. Thirty-Day Clinical Outcomes.

	Non-Complex – Class A/B1 (N = 3093)	Complex – Class B2/C (N = 5423)	Adjusted HR* (95% CI)	p Value*
Target lesion failure†	1.1% (34)	2.0% (107)	1.90 (1.22, 2.96)	0.004
Major adverse cardiac events‡	1.2% (37)	2.0% (109)	1.82 (1.18, 2.79)	0.006
Target vessel failure§	1.3% (39)	2.0% (110)	1.66 (1.10, 2.51)	0.016
Death(*)	0.1% (4)	0.3% (15)	1.67 (0.55, 5.07)	0.37
Cardiac(*)	0.0% (1)	0.2% (13)	5.31 (0.69, 40.73)	0.11
Non-cardiac(*)	0.1% (3)	0.0% (2)	0.36 (0.06, 2.22)	0.27
Myocardial infarction	1.1% (34)	1.7% (90)	1.66 (1.06, 2.59)	0.025
Target vessel	1.0% (31)	1.6% (88)	1.74 (1.10, 2.76)	0.018
Periprocedural	0.9% (28)	1.4% (75)	1.60 (0.98, 2.60)	0.059
Target lesion revascularization(*)	0.3% (5)	0.5% (14)	1.87 (0.79, 4.39)	0.15
Target vessel revascularization(*)	0.4% (13)	0.5% (27)	1.16 (0.59, 2.28)	0.66
Stent thrombosis(*)	0.2% (6)	0.3% (18)	1.56 (0.62, 3.96)	0.35
Definite(*)	0.2% (6)	0.3% (14)	1.24 (0.47, 3.25)	0.66
Probable(*)	0% (0)	0.1% (4)	N/A	N/A

*denotes there were too few events to adjust the HR, and thus a univariate HR is presented. † denotes the composite of cardiac death, ischemia-driven target lesion revascularization, and target vessel-myocardial infarction. ‡ denotes the composite of cardiac death, ischemia-driven target lesion revascularization, and any myocardial infarction. § denotes the composite of cardiac death, target vessel-myocardial infarction, and ischemia-driven target vessel revascularization. CI = confidence interval; HR = hazard ratio.

Table S3. One- and 5-Year Clinical Outcomes According to ACC/AHA Class.

	Class A (n=732)	Class B1 (n=2991)	Class B2 (n=3875)	Class C (n=3925)	Overall p Value
1 year					
Target lesion failure*	2.1% (14)	3.2% (78)	3.9% (111)	5.4% (138)	<0.0001
Major adverse cardiac events†	2.4% (16)	3.3% (79)	4.0% (113)	5.6% (142)	<0.0001
Target vessel failure‡	2.6% (17)	4.2% (101)	5.0% (142)	6.0% (153)	0.0005
Death	1.7% (11)	1.0% (23)	1.5% (42)	1.9% (48)	0.050
Cardiac	0.8% (5)	0.5% (11)	1.0% (28)	1.0% (25)	0.12
Non-cardiac	0.9% (6)	0.5% (12)	0.5% (14)	0.9% (23)	0.15
Myocardial infarction	0.6% (4)	1.7% (40)	1.7% (50)	2.9% (74)	0.0002
Target vessel	0.3% (2)	1.6% (39)	1.7% (48)	2.7% (69)	0.0001
Target lesion revascularization (ID)	1.1% (7)	1.5% (37)	1.9% (54)	2.4% (60)	0.059
Target vessel revascularization (ID)	1.7% (11)	2.6% (62)	3.1% (87)	3.0% (76)	0.19
Stent thrombosis	0.0% (0)	0.3% (8)	0.6% (18)	0.5% (12)	0.12
Definite	0.0% (0)	0.3% (8)	0.6% (16)	0.3% (7)	0.11
Probable	0.0% (0)	0.0% (0)	0.1% (2)	0.2% (5)	0.08
5 years					
Target lesion failure*	6.8% (36)	9.9% (193)	11.2% (268)	13.7% (293)	<0.0001
Major adverse cardiac events†	7.5% (40)	10.5% (207)	12.3% (288)	14.7% (313)	<0.0001
Target vessel failure‡	11.0% (55)	13.0% (254)	13.9% (333)	15.8% (336)	0.0007
Death	8.3% (40)	7.2% (118)	8.1% (176)	8.4% (154)	0.24
Cardiac	2.9% (14)	2.9% (48)	3.4% (77)	4.3% (84)	0.03
Non-cardiac	5.5% (26)	4.4% (70)	4.8% (99)	4.3% (70)	0.31
Myocardial infarction	1.2% (7)	3.7% (77)	4.6% (111)	5.9% (130)	<0.0001
Target vessel	0.5% (3)	3.0% (62)	3.4% (89)	4.8% (108)	<0.0001
Target lesion revascularization (ID)	3.8% (21)	5.8% (112)	6.5% (148)	7.5% (151)	0.02
Target vessel revascularization (ID)	8.2% (41)	9.5% (181)	9.8% (227)	10.2% (205)	0.38
Stent thrombosis	0.5% (3)	0.8% (15)	1.5% (34)	2.2% (38)	0.008
Definite	0.5% (3)	0.5% (12)	1.2% (29)	1.5% (26)	0.08
Probable	0.0% (0)	0.3% (3)	0.3% (5)	0.7% (12)	0.02

Values are % (n). Values are % (n). *The composite of cardiac death, target vessel-related myocardial infarction, or ischemia-driven (ID) target lesion revascularization; †the composite of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization; ‡the composite of cardiac death, target vessel-related myocardial infarction, or ischemia-driven target vessel revascularization.

Table S4. Univariate and Multivariable Analysis for Predictors of Target Lesion Failure at 5 Years.

	Univariable Model		Multivariable Model	
Variable	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
ACC/AHA class B2/C vs. A/B1	1.42 (1.21, 1.66)	<0.0001	1.39 (1.17-1.64)	0.0001
Age (per year)	1.01 (1.01-1.02)	<0.0001	1.01 (1.00-1.02)	0.035
Male sex	0.91 (0.79-1.06)	0.24	0.96 (0.81-1.13)	0.64
Diabetes	1.64 (1.41, 1.91)	<0.0001	1.50 (1.26-1.78)	<0.0001
Hypertension	1.25 (1.07, 1.45)	0.005	1.12 (0.94-1.33)	0.22
Hyperlipidemia	1.09 (0.93, 1.26)	0.29	0.95 (0.80-1.13)	0.59
Prior CABG	2.36 (1.95, 2.87)	<0.0001	2.01 (1.61-2.51)	<0.0001
Prior MI	1.35 (1.15, 1.58)	0.0002	1.16 (0.97-1.40)	0.11
Prior PCI	1.37 (1.16, 1.61)	0.0002	1.13 (0.93-1.37)	0.21
Body mass index (per kg/m^2)	1.02 (1.01, 1.03)	0.002	1.01 (1.00-1.03)	0.056
ACS vs. stable CAD	0.88 (0.76, 1.03)	0.11	1.01 (0.86-1.19)	0.86

ACC = American College of Cardiology; ACS = acute coronary syndromes; AHA = American Heart Association; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.