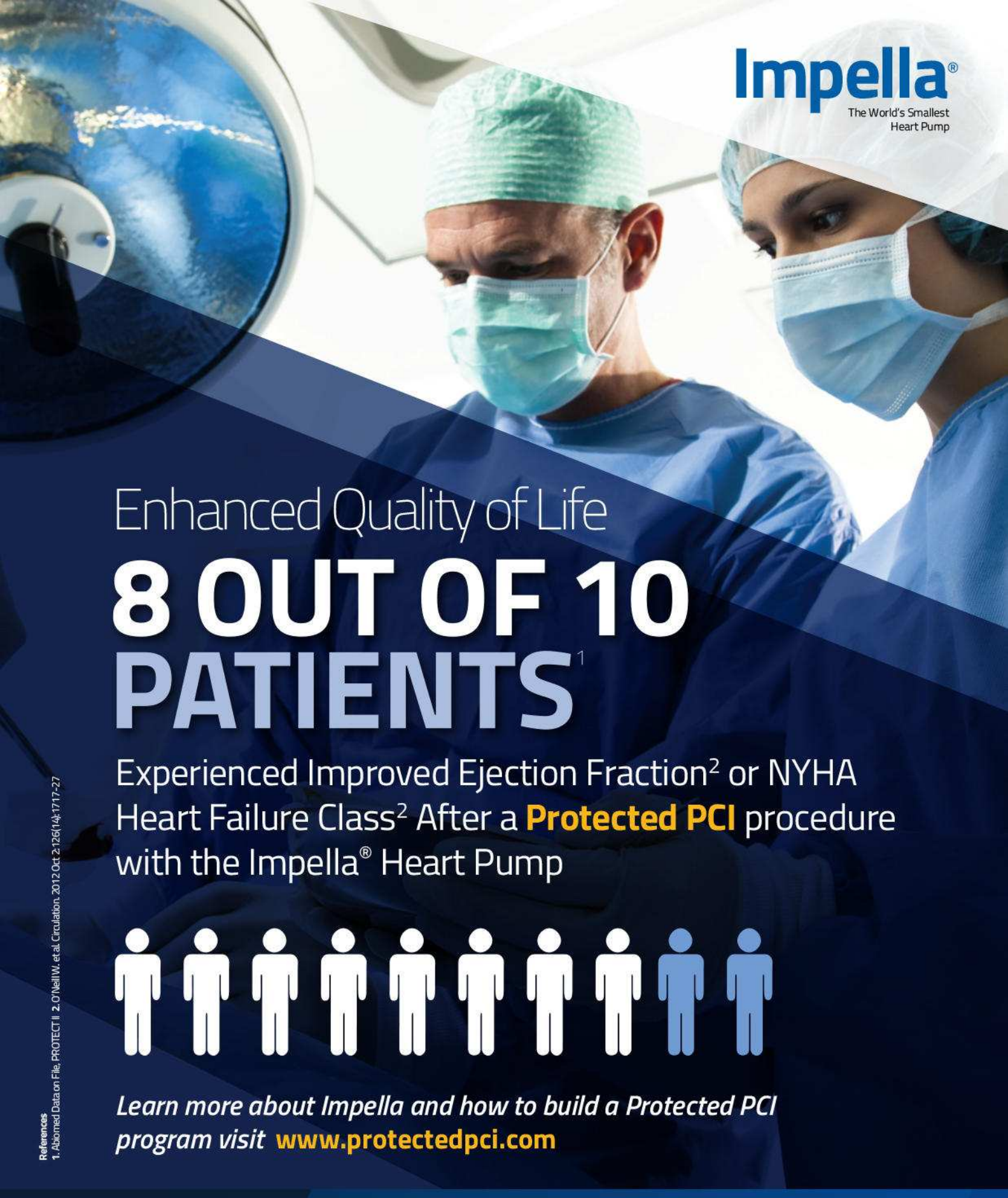

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DOI: 10.1111/j.1540-8183.2012.00753.x

DRUG ELUTING STENTS

Use and Misuse of Multivariable Approaches in Interventional Cardiology Studies on Drug-Eluting Stents: A Systematic Review

FABRIZIO D'ASCENZO, M.D.,[1] ERIKA CAVALLERO, M.D.,[1] GIUSEPPE BIONDI-ZOCCAI, M.D.,[2] CLAUDIO MORETTI, M.D., PH.D.,[1] PIERLUIGI OMEDÈ, M.D.,[1] MARIO BOLLATI, M.D.,[1] DAVIDE CASTAGNO, M.D.,[1] MARIA GRAZIA MODENA, M.D.,[2] FIORENZO GAITA, M.D.,[1] and IMAD SHEIBAN, M.D.[1]

From the [1]Division of Cardiology, University of Turin, Turin, Italy; and [2]Division of Cardiology, University of Modena and Reggio Emilia, Modena, Italy

Aims: *Randomized clinical trials (RCTs) are the most reliable evidence, even if they require important resource and logistic efforts. Large, cost-free and real-world datasets may be easily accessed yielding to observational studies, but such analyses often lead to problematic results in the absence of careful methods, especially from a statistic point of view. We aimed to appraise the performance of current multivariable approaches in the estimation of causal treatment and effects in studies focusing on drug-eluting stents (DES).*

Methods and Results: *Pertinent studies published in the literature were searched, selected, abstracted, and appraised for quality and validity features. Six studies with a logistic regression were included, all of them reporting more than 10 events for covariates and different length of follow-up, with an overall low risk of bias. Most of the 15 studies with a Cox proportional hazard analysis had a different follow-up, with less than 10 events for covariates, yielding an overall low or moderate risk of bias. Sixteen studies with propensity score were included: the most frequent method for variable selection was logistic regression, with underlying differences in follow-up and less than 10 events for covariate in most of them. Most frequently, calibration appraisal was not reported in the studies, on the contrary of discrimination appraisal, which was more frequently performed. In seventeen studies with propensity and matching, the latter was most commonly performed with a nearest neighbor-matching algorithm yet without appraisal in most of the studies of calibration or discrimination. Balance was evaluated in 46% of the studies, being obtained for all variables in 48% of them.*

Conclusions: *Better exploitation and methodological appraisal of multivariable analysis is needed to improve the clinical and research impact and reliability of nonrandomized studies.* (J Interven Cardiol 2012;25:611–621)

Introduction

Randomized clinical trials (RCTs) generate the most reliable clinical evidence,[1] especially when combined within systematic reviews or meta-analyses. Despite these strengths, they deserve a critical appraisal[2] about their methodological rigor, to stress their most relevant limits like analysis of highly selected patients, subject attrition, and event adjudication.

Thus, also in interventional cardiology, still a high number of nonrandomized studies are performed in order to save economical resources,[3] to create hypothesis, especially for nonrandomizable patients, or to shed light on the generalizability of results from existing randomized experiments.[4]

In the attempt to exploit the broad potential resources of observational databases, various statistical models are currently employed. Several different multivariable approaches are available to control for systematic

Address for reprints: Dr. Fabrizio D'Ascenzo, Division of Cardiology, University of Turin, S. Giovanni Battista "Molinette" Hospital, Corso Bramante 88–90, 10126 Turin, Italy. Fax: 0016335419; e-mail: fabrizio.dascenzo@gmail.com

Table 1. Statistical Features of Studies with Logistic Regression

Studies	N = 6
Time of Publication	2007 (2006–2009)
Study design	
– Retrospective	3 (50%)
– Prospective	3 (50%)
Study organization	
– One center	3 (50%)
– Multicenter	3 (50%)
Data source	
– Clinical database	6 (100%)
Follow-up	
Similar	3 (50%)
Nonsimilar	3 (50%)
Censored data	
Yes	5 (83%)
No	1 (7%)
Number of events for covariate	
Less than 10	0 (100%)
Analytical bias	
Low risk	8 (61%)
Moderate risk	5 (39%)
High or unclear risk	0
Selection bias	
Low risk	2 (14%)
Moderate risk	4 (86%)
Adjudication bias	
Low risk	3 (50%)
Moderate risk	3 (50%)
Attrition bias	
Low risk	5 (83%)
Moderate risk	1 (7%)
Overall credibility	
Moderate	4 (86%)
High	2 (15%)

Table 2. Statistical Features of Studies with Cox Proportional Hazard Analysis

Studies	N = 15
Time of Publication	2008 (2008–2009)
Study design	
– Retrospective	7 (46%)
– Prospective	8 (54%)
Study organization	
– One center	10 (69%)
– Multicenter	5(31%)
Data source	
– Clinical database	15 (100%)
Follow-up	
Similar	2 (12%)
Nonsimilar	13 (88%)
Censored data	
Yes	14 (94%)
No	1 (6%)
Number of events for covariate	
Less than 10	10 (60%)
More than 10	4 (24%)
Unclear	1 (6%)
Analytical bias	
Low risk	9 (74%)
Moderate risk	6 (36%)
Selection bias	
Low risk	8 (48%)
Moderate risk	7 (42%)
Adjudication bias	
Low risk	4 (24%)
Moderate risk	8 (48%)
Unclear	3 (18%)
Attrition bias	
Low risk	3 (18%)
Moderate risk	9 (54%)
Unclear	3 (18%)
Overall credibility	
Moderate	12 (82%)
High	2 (12%)
Very high	1 (6%)

baseline differences between groups naturally occurring in the nonrandomized setting.[5] Even more their striking importance lies on defining the impact of several independent variables on a single dependent variable, thus avoiding confounding effects coming from observed variables in nonrandomized studies.

Nevertheless multivariable analysis should be performed according to precise statistical issues,[6–12] to assure accurate and understandable results, and to offer a more pregnant impact on everyday practice.

To our knowledge, no systematic review was performed to assess bulk and quality of multivariable approaches in observational studies, focusing on the comparison between drug-eluting stents (DES) versus bare metal stents (BMS) for percutaneous coronary intervention (PCI). Given this purpose, we explored the methodological structure of articles, assessed how often authors explicitly faced the topic of internal validity, tested the risk for different bias, and, finally, aimed to propose a score to summarize the overall credibility of nonrandomized studies

Methods

PubMed was searched for pertinent articles published between January 2002 (when DES were first marketed worldwide) and December 2010 in keeping with established methods,[13] searching for:

Table 3. Statistical Features of Studies with Propensity Score

Studies	N = 16
Time of Publication	2008 (2008–2009)
Study design	
Retrospective	5 (32%)
Prospective	11 (68%)
Study organization	
One center	10 (63%)
Multicenter	6 (37%)
Data source	
Clinical database	14 (84%)
Institutional database	2 (16%)
Follow-up	
Similar	2 (12%)
Nonsimilar	14 (84%)
Censored data	
Yes	13 (76%)
No	3 (24%)
Number of events for covariate	
Less than 10	5 (30%)
More than 10	11 (70%)
Methods to select variables	
Logistic regression model	16 (100%)
Variables inserted according to	
Nonparsimonious	7 (42%)
Selected variables	11 (68%)
Propensity score included in Cox multivariable analysis.	5 (30%)
Discrimination appraisal	
Not reported	6 (48%)
Reported (median and third quartiles of c-index)	10 (52%) 0.87 (0.82–0.86)
Calibration appraisal	
Not reported	9 (48%)
Reported not significant according to Hosmer-Lemeshow test	7 (42%)
Collinearity appraisal	
Not reported	16 (100%)
Analytical bias	
Low risk	10 (64%)
Moderate risk	6 (36%)
Selection bias	
Low risk	9 (54%)
Moderate risk	6 (36%)
Unclear	1 (6%)
Adjudication bias	
Low risk	7 (42%)
Moderate risk	6 (36%)
Unclear	3 (18%).
Attrition bias	
Low risk	3 (18%)
Moderate risk	9 (54%)
Unclear	3 (18%)
Overall credibility	
Moderate	12 (82%)
High	2 (12%)
Very high	1 (6%)

- DES and BMS* and multivariate analysis
- DES and BMS* and multivariable methods
- DES and BMS* and logistic regression
- DES and BMS* and Cox proportional hazard analysis
- DES and BMS* and propensity score
- DES and BMS* and propensity score with matching

Study Selection. Retrieved citations were first screened independently by 2 reviewers (G.B.-Z, F.DA.) at the title and/or abstract level, with divergences resolved after consensus. If potentially pertinent, they were then appraised as complete reports according to the following explicit selection criteria, which were piloted over the first 5 cases for consistency and discrimination. Inclusion criteria were (all had to be met for inclusion): (i) human studies, with nonrandomized design (ii) investigating patients undergoing PCI, with implantation of DES and BMS, and (iii) employing multivariable approaches. Exclusion criteria were (any one alone was enough for exclusion): (i) nonhuman setting and (ii) RCT design. No dimensional cut off in terms of included patients was used, to offer a wide representation of interventional studies.

Data Extraction. The following data were abstracted by 2 unblinded independent reviewers (G.B.-Z, F.DA.) on prespecified forms, which were piloted over the first 5 cases for consistency and discrimination, with divergences resolved after consensus. In particular, authors, journal, year of publication, location of the study group were first assessed, and impact on death, myocardial infarction (MI), repeat revascularization, or their composite, namely major adverse cardiac events (MACE).

Statistical Methods Appraisal. Studies responding to inclusion criteria were divided according to their multivariable approaches[12] in logistic regression, Cox proportional hazard analysis, propensity score and propensity score with matching. First, for all of these studies evaluation of difference in follow-up length, presence of censored data, and number of events per covariates was performed. Then, for studies with propensity score adjustment, we analyzed methods for variable selection, prediction, discrimination, calibration collinearity, and use of parsimonious or not approach.[8] Then, if matching was present, matching methods and balance were also analyzed.

Table 4. Statistical Features of Studies with Propensity Score with Matching

Studies Time of Publication	N = 17 2008 (2007–2009)
Study design	
Retrospective	7 (45%)
Prospective	10 (55%)
Study organization	
One center	12 (75%)
Multicenter	5 (25%)
Data source	
Clinical database	15 (79%)
Institutional database	2 (11%)
Follow-up	
Similar	2 (11%)
Nonsimilar	15 (79%)
Censored data	
Yes	17 (100%)
Number of events for covariate	
Less than 10	9 (55%)
More than 10	8 (45%)
Methods to select variables	
Logistic regression model	15 (79%)
Unclear	2 (21%)
Variables inserted according to	
Nonparsimonious	3 (16%)
Selected variables	13 (64%)
Unclear	1 (5.5%)
Propensity score included in Cox multivariable analysis	3 (16%)
Matching method	
Nearest-neighbor–matching algorithm	14 (78%)
Quintiles	2 (12%)
Unclear	1 (6%)
Balance assessment	
Performed, with differences less than 10%	6 (40%)
Performed, with differences less than 5%	1 (6%)
Unclear	6 (54%)
Balance achieved for	
All variables	8(48%)
All except	
■ 1 variable	1 (6%)
■ 2 variables	1 (6%)
■ 3 variables	1 (6%)
■ 4 variables	2 (12%)
■ 8 variables	1 (6%)
Nonreported	3 (18%)
Discrimination appraisal	
Not reported	11 (63%)
Reported (median and third quartiles of c-index)	6 (37%)
Calibration appraisal	
Not reported	15 (89%)
Reported not significant according to Hosmer-Lemeshow test	2 (11%)
	0.73 (0.71–0.76)
Collinearity appraisal	
Not reported	14 (78%)
Reported, without reporting high correlation	3 (22%)
Analytical bias	
Low risk	13 (78%)
Moderate risk	4 (22%)
Selection bias	
Low risk	7 (42%)
Moderate risk	10 (58%)
Adjudication bias	
Low risk	7 (42%)
Moderate risk	9 (52%)
Unclear	1 (6%).
Attrition bias	
Low risk	5 (30%)
Moderate risk	8 (48%)
Unclear	2 (12%)
Overall credibility	
Moderate	9 (54%)
High	6 (36%)
Very high	2 (10%)

Internal Validity and Quality Appraisal. The quality of included studies was appraised by unblinded independent reviewers (G.B.-Z, F.DA.), on prespecified forms, which were piloted over the first 5 cases for consistency and discrimination, with divergences resolved after consensus. Modifying the MOOSE (Meta-analysis of Observational Studies in Epidemiology) items to take into account the specific features of included studies,[4] we separately abstracted and appraised study design, setting, data source, and statistical methods for multivariable analysis, as well as risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias). Moreover, we appraised the overall credibility of short listed studies, to summarize the previous features. Zero points were assigned for retrospective design and single-center setting, 1 for prospective design and for a multicenter setting. Moreover, 2 points were ascribed for overall low risk of bias, 1 for moderate risk, and zero for high or unclear risk. If the sum of these scores was 10, a very high credibility was granted; if it was between 7 and 9, high; 4 and 6, moderate; 1 and 3, low; 0, very low (e.g., a multicenter study with prospective design, with low risk of analytical bias, medium risk of selection bias, low of attrition bias, medium of adjudication

bias totally scored 9, thus with high credibility; for further details, see Table S1). Moreover, for studies with propensity score and with propensity score with matching, distribution of statistical features among studies with moderate and high quality, and among studies in different quartiles of Impact Factor (IF; CI 95%) was evaluated.

Data Analysis and Synthesis. Continuous variables are reported as mean (standard deviation) or median (range). Categorical variables are expressed as n/N (%). No formal test of hypothesis was employed given the exploratory and hypothesis generating scope of our systematic review.

Results

Fifty-eight studies were initially analyzed: 3 were excluded for reporting only multivariable analysis results,[14–16] 2 because reporting only predictors of stent thrombosis,[17,18] 3 because noncomparing directly BMS and DES[19–22]; finally 50 studies were included (Fig. 1).

Six studies with a logistic regression were included,[23–28] all of them reporting more than 10 events for covariates and different length of follow-up, with an overall low risk of bias (Table 1). Logistic regression did not modify results of univariate analysis. (Fig. 2).

Fifteen studies with a Cox proportional hazard analysis[25,29–42] are described in Table 2. Eighty-eight percent of them had different follow-up, 94% censored data and 60% reported less than 10 events for covariates. An overall low or moderate risk of bias was appraised. At multivariate analysis, superiority for DES in reducing myocardial infarction and death was less frequently reported (Fig. 3).

Sixteen studies with propensity score were analyzed[34,42–56] (Table 3). Logistic regression was always used for variable selection; 84% of them reported differences in follow-up, 70% more than 10 events for covariate and a nonparsimonious method of variable selection was noted in 42% of cases. Both calibration and discrimination appraisal were reported in 52% of the studies; moreover, propensity score was inserted in Cox multivariable analysis in 30% of cases. Overall analysis showed no differences between BMS and DES, after multivariable analysis in most cases for death and myocardial infarction (Fig. 4).

In the 17 included studies,[57–73] matching was performed with a nearest neighbor-matching algorithm in 78% of cases (Table 4). Variables were inserted with a nonparsimonious method in 16% of cases, and balance was evaluated in 46% of studies, being obtained for all variables in 48% of them; discrimination was reported in 37% and calibration in 11% of cases. Myocardial infarction and death trended to change, the former without differences between BMS and DES after propensity score with matching, the latter showing a tendency to better outcome after stenting with DES (Fig. 5).

Interestingly, both after appraisal for IF and quality differences only small differences were found for propensity score with matching about discrimination, calibration, and balance evaluation among different classes (Figs. 6, 7 and 8). On the contrary, for propensity scores studies within the highest quartiles of IF, calibration and discrimination were most frequently reported.

Discussion

The present review originally shows for the first time that the application of complex multivariable methods is becoming increasingly popular in nonrandomized medical research. Yet, statistical analyses of these studies often lack internal appraisal and validation, a finding approximately independent from the rating of the journal in which the studies were published. Evaluation of the methodological quality of such studies through a synthetic score is feasible and appears important for a critical approach to medical literature.

Because of great economical and medical policy changes[3] observational studies will gain room in scientific research, and the next era has indeed been defined as the time of comparative-effectiveness research. RCTs remain the leading evidence; being burdened from several economical, logistic, and temporal hurdles, these costs cannot generate bias-free information anyway.[74–76] Moreover, given the international economic scenario and the growing role of conflict of interest in data interpretation,[77,78] researchers ought to develop new tools to prevent problems affecting the accuracy and interpretation of results obtained from widely available observational datasets. As a matter of fact, such a kind of methodological problem would make the reported results potentially inaccurate, misleading, or difficult to interpret.

From our review of current literature, multivariable analysis is the reference method to explore observational information equally in its different approaches

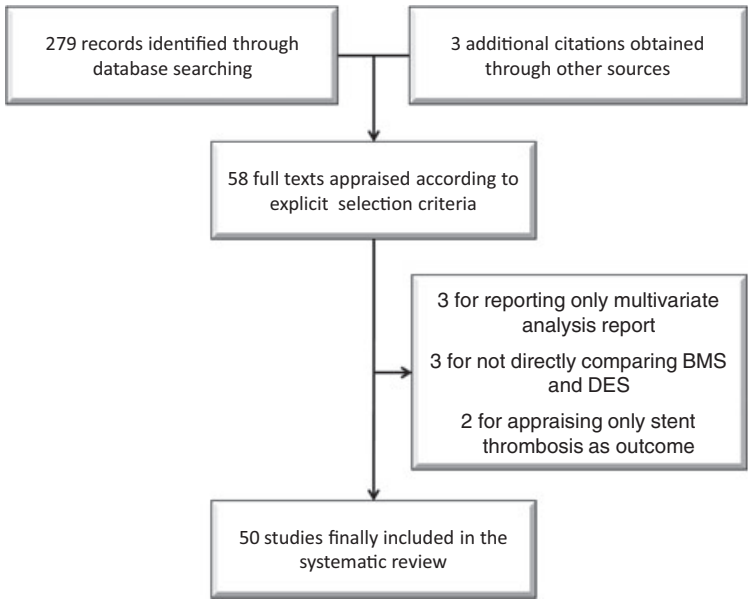

Figure 1. Review's profile.

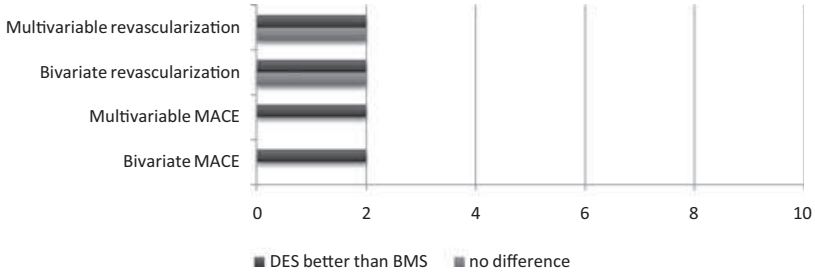

Figure 2. Performance of logistic regression studies. (DES = Drug-eluting stent; BMS = Bare metal stent). Red lines represented studies reporting first at univariate, then at multivariate analysis, a significant better outcome for DES, blue lines for BMS.

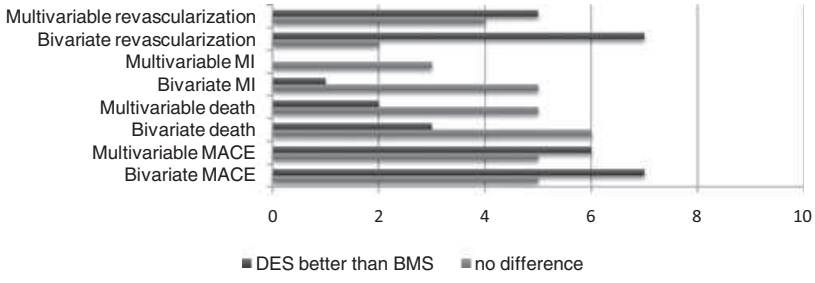

Figure 3. Performance of Cox proportional hazard analysis studies. Red lines represented studies reporting first at univariate, then at multivariate analysis, a significant better outcome for DES, blue lines for BMS.

(logistic regression, Cox proportional hazard analysis, propensity score, or propensity score with matching and multiple logistic regression). All the examined statistical methods tend to approach observational studies results to meta-analysis outcomes: actually BMS did not show, after multivariable approaches, a detrimental effect on survival, as demonstrated in 2 recent systematic reviews.[79,80] Thus, to give more statistical significance to this analysis, it is worthwhile to critically appraise and develop their internal validity, both for the point of view of reducing risk of bias and for the point of view of statistical analysis.[8–11] Actually, as with all scientific models the results require validation to ensure protection against unrecognized problems and limitations.

Unfortunately, our results underline an overall moderate risk of adjudication and attrition bias, while the risk of selection and analytical bias seemed less pronounced. The chance to overcome adjudication- and attrition-related pitfalls may lie in example in a more

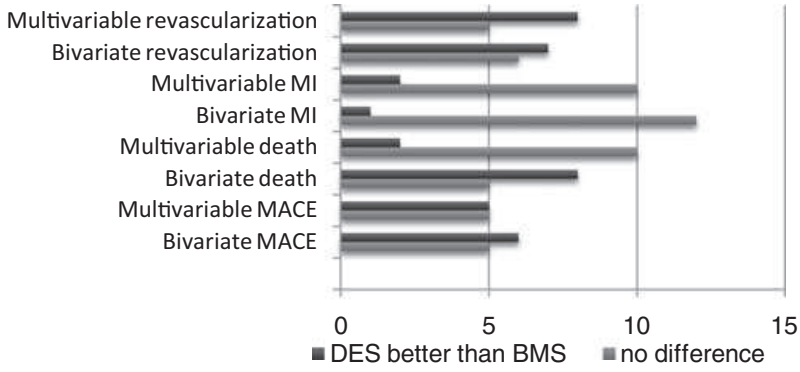

Figure 4. Performance of propensity score studies. Red lines represented studies reporting first at univariate, then at multivariate analysis, a significant better outcome for DES, blue lines for BMS.

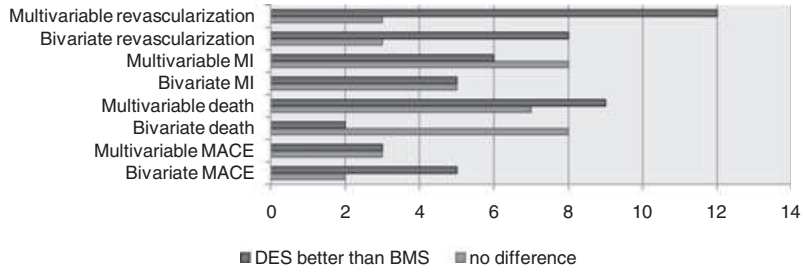

Figure 5. Performance of propensity score studies with matching. Red lines represented studies reporting first at univariate, then at multivariate analysis, a significant better outcome for DES, blue lines for BMS.

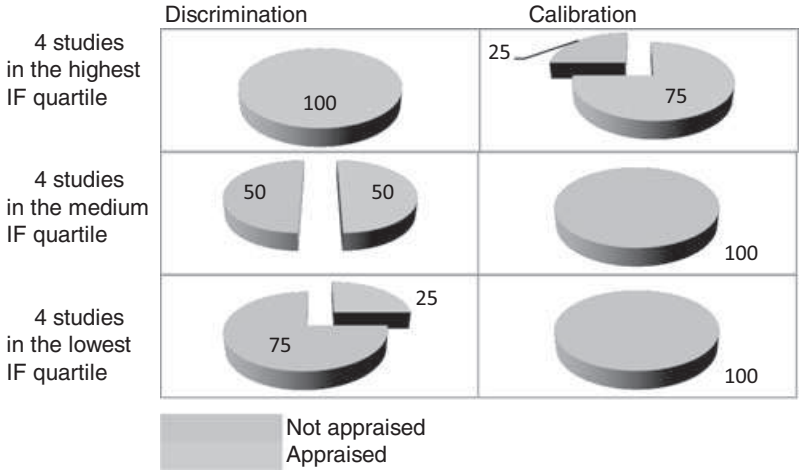

Figure 6. Discrimination and calibration appraisal according to Impact factor of propensity studies. Four were included in the lowest quartile (with an IF < 2.80), four in the highest (IF > 6.80), and four with IF between previous values. Four studies were inserted in not impacted Journal.

detailed definition of end-points, in the assignment of events by 2 blinded experienced researchers and in intention to treat analysis.

The same criticism suits statistical analysis because a low number of events per variable was a common feature among the screened studies, potentially suggesting overfitted data and misleading associations.[75] Another tricky finding of the present review is the lack of reporting and perhaps conducting of internal control, as frequently it was not possible to assess calibration or censoring appraisal.[6,74]

Finally, omission of the methodological assessment was not related to quality rating of the journal in which the paper was published: we found no substantial differences among studies stratified according to journal of publication IF, thus stressing also more careful attention from peer reviewers in studies reporting multivariable adjustments.

The main implication of our remarks is a call for researchers to improve the reports about their statistical analysis with care for internal validation and methodological assessment. Our score may be useful to fulfill

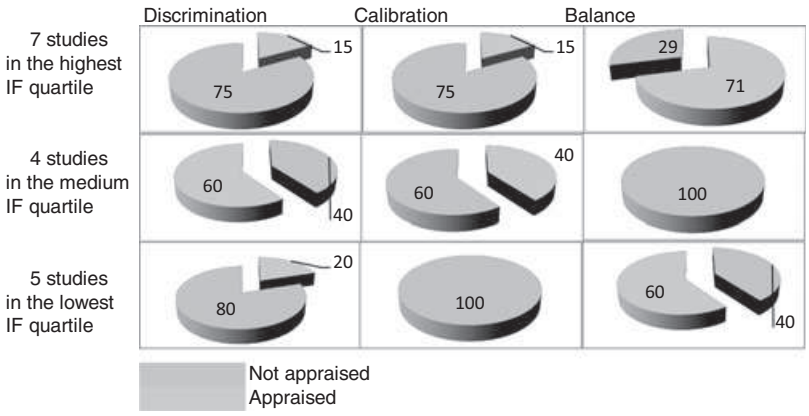

Figure 7. Discrimination, calibration and balance appraisal according to Impact factor of propensity studies with matching. Five were included in the lowest quartile (with an IF < 5.24), seven in the highest (IF > 14.82) and four with IF between previous values. One study was inserted in not impacted Journal.

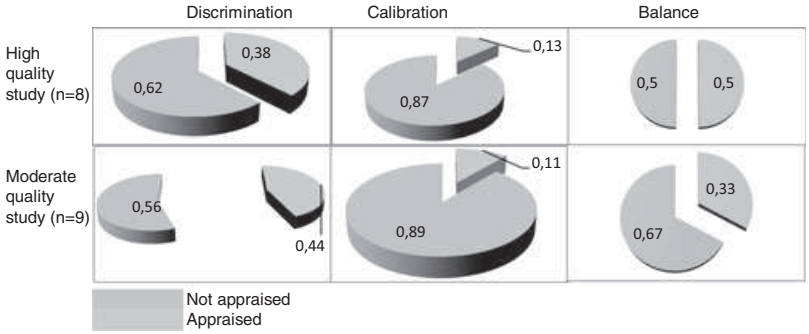

Figure 8. Discrimination, calibration, and balance appraisal according to propensity score with matching studies' quality.

this aim, helping investigators and reviewers to guide and correct themselves.

Possible limitation of the present investigation is the variety of involved studies that broadly differ in the number of patients included, follow-up length, and year of publication. Anyway, we consider these limitations avenues for further research because it would be interesting to evaluate the methodological quality of medical research in relation to study dimensions and the period of realization.

In summary, multivariate analysis is spreading around in medical literature, and as a useful tool to exploit observational data it needs a more detailed internal control. For readers, clinicians, and researchers a simple assessment of methodology is fundamental to drive critical and conscious employment of scientific information.

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Supporting Information

Additional supporting information may be found in the online version of this article.

Table S1. Appendix Web Only Table

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