European Heart Journal (2015) **36**, 94–99
doi:10.1093/eurheartj/ehu383

Interventional cardiology

Prognostic role of restenosis in 10 004 patients undergoing routine control angiography after coronary stenting

Salvatore Cassese[1], Robert A. Byrne[1], Stephanie Schulz[1], Petra Hoppman[2], Johanna Kreutzer[1], Antonia Feuchtenberger[1], Tareq Ibrahim[2], Ilka Ott[1], Massimiliano Fusaro[1], Heribert Schunkert[1], Karl-Ludwig Laugwitz[2], and Adnan Kastrati[1]*

[1]Deutsches Herzzentrum, Technische Universität München and DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Lazarettstrasse, 36, Munich, Germany; and [2]1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München and DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

Received 14 June 2014; revised 14 August 2014; accepted 21 August 2014; online publish-ahead-of-print 8 October 2014

See page 71 for the editorial comment on this article (doi:10.1093/eurheartj/ehu398)

Aim Routine control angiography is a valuable tool with high-sensitivity in detecting restenosis after coronary stenting. However, the prognostic role of restenosis is still controversial. We investigated the impact of restenosis on 4-year mortality in patients undergoing routine control angiography after coronary stenting.

Methods and results All the patients undergoing successful implantation of coronary stents for *de novo* lesions from 1998 to 2009 and routine control angiography after 6–8 months at two centres in Munich, Germany were studied. Restenosis was defined as diameter stenosis ≥50% in the in-segment area at follow-up angiography. The primary outcome was 4-year mortality. The study included 10 004 patients with 15 004 treated lesions. Restenosis was detected in 2643 (26.4%) patients. Overall, there were 702 deaths during the follow-up. Of these, 218 deaths occurred among patients with restenosis and 484 deaths occurred among patients without restenosis [unadjusted hazard ratio: HR: 1.19; (95% confidence interval CI: 1.02–1.40); $P = 0.03$]. The Cox proportional hazards model adjusting for other variables identified restenosis as an independent correlate of 4-year mortality [HR: 1.23; (95% CI: 1.03–1.46); $P = 0.02$]. Other independent correlates of 4-year mortality were age [for each 10-year increase, HR: 2.34; (95% CI: 2.12–2.60); $P < 0.001$], diabetes mellitus [HR: 1.68; (95% CI: 1.41–1.99); $P < 0.001$], current smoking habit [HR: 1.39; (95% CI: 1.09–1.76); $P = 0.01$], and left ventricular ejection fraction [for each 5% decrease, HR: 1.39; (95% CI: 1.31–1.48); $P < 0.001$].

Conclusions In this large cohort of patients, the presence of restenosis at follow-up angiography after coronary stenting was predictive of 4-year mortality. Whether routine control angiography after coronary stenting is beneficial and influences outcomes should be evaluated by properly designed randomized trials.

Keywords Angiography • Coronary artery disease • Restenosis • Mortality

Introduction

In patients undergoing percutaneous coronary intervention (PCI), the use of drug-eluting stent (DES) considerably reduced the need for reinterventions when compared with bare metal stent (BMS).[1] However, the occurrence of restenosis, the re-narrowing of a coronary artery at the stented segment, remains the principal reason for failure of contemporary percutaneous revascularization therapies.[2]

The use of routine control angiography to detect restenosis is an important tool in the characterization of vascular response to different stent types and an integral part of many comparative efficacy studies.[3–6] Notwithstanding this, the prognostic role of restenosis

* Corresponding author. Tel: +49 8912184577, Fax: +49 8912184053, Email: kastrati@dhm.mhn.de

detected at routine control angiography after coronary stenting still remains controversial.

Previous studies investigating the clinical impact of routine control angiography showed no benefits in terms of long-term survival.[7,8] For this reason, guideline-writing authorities and appropriate use criteria restricted recommendation of control angiography to patients complaining of anginal symptoms or presenting signs of ischaemia.[9] In some other studies, patients with angiographically proved restenosis at routine surveillance showed a worse prognosis at long-term follow-up.[10–12]

Given the lack of definitive conclusions, we sought to investigate the prognostic role of restenosis in a large broadly inclusive population undergoing routine control angiography after PCI with stenting.

Methods

All the patients with coronary artery disease receiving a coronary stent for *de novo* lesions between January 1998 and December 2009 and undergoing routine control angiography at 6–8 months after successful intervention in two tertiary-referral centres in Munich, Germany (*Deutsches Herzzentrum* and *1. medizinische Klinik, Klinikum rechts der Isar*) were eligible for this study. A routine follow-up angiography at this time point after revascularization is the standard clinical practice at these centres. Patients with cardiogenic shock, chronic renal replacement therapy, or previous cardiac transplantation were excluded. Bare metal stents were the sole platforms implanted from January 1998 to August 2002; thereafter, DES became available. Full description of the stent platforms used at the time of index PCI has been reported previously.[1] At the time of index intervention, all the patients received aspirin as well as a loading dose of platelet adenosine-diphosphate receptor inhibitors; at discharge, aspirin therapy was recommended indefinitely, while platelet adenosine-diphosphate receptor inhibitors were prescribed for a period of time ranging from 1 to 24 months, depending on clinical presentation or type of stent implanted. All study subjects received standard cardioactive therapies as indicated (e.g. beta-blockers, statins, angiotensin-converting enzyme inhibitors, and other drugs). Further details of the study population have been previously reported.[1]

Coronary angiography evaluation and definitions

Restenosis (angiographic or binary) was defined as diameter stenosis $\geq$50% in the in-segment area (including the stent area and 5-mm segments proximal and distal to the stent edges). The presence of restenosis at control angiography was assessed off-line in the quantitative angiographic core laboratory (*ISARESEARCH Center, Munich, Germany*) with an automated edge-detection system (*Medis Medical Imaging Systems, Leiden, Netherlands*) by independent experienced operators, as previously reported.[1]

In case of restenosis at routine follow-up angiography, the decision to perform a target vessel revascularization (TVR) was left to operator discretion based on the clinical evaluation, the recurrence of symptoms and/or proof of ischaemia.

The primary outcome of this analysis was 4-year mortality. After routine control angiography, the follow-up information out to 4 years was obtained by a telephone call at 30 days, a hospital visit at 6 months, a telephone call at 1 year, and annual telephone calls or office visits thereafter. Patients who had cardiac complaints underwent a complete clinical, electrocardiographic, and laboratory evaluation. Information about death was obtained from hospital records, death certificates, or telephone contact with relatives of the patient or referring physician. The follow-up information was obtained by personnel blinded to the clinical characteristics of the patients.

Statistical analysis

Categorical data are presented as counts and proportions (%) and were compared with the χ^2 test. Continuous data were tested for normality of distribution using the Kolmogorov–Smirnov test. If normality was not rejected, data are presented as mean $\pm$ standard deviation and comparisons were performed with the use of Student's *t*-test; otherwise data are presented as median and inter-quartile range (25th; 75th percentiles) and compared using the Wilcoxon rank-sum test. Four-year mortality was estimated by applying the Kaplan–Meier method and the log-rank test, which allowed the calculation of hazard ratios (HR) with 95% confidence intervals (CI) and respective *P*-values associated with the presence of restenosis at routine control angiography. Multivariable Cox proportional hazards models adjusted for potential confounding variables were used to assess the independent role of restenosis in determining the risk for death at 4 years after routine control angiography. We included in the model all clinical features reporting a difference between the group with and without angiographic restenosis with a *P*-value <0.05 at univariate analysis plus age, body mass index, hypertension, hypercholesterolaemia, current smoke habit, previous myocardial infarction, and baseline left ventricular ejection fraction. Multicollinearity was assessed by calculating the variance inflation factor (VIF) for each predictor. A VIF between 5 and 10 indicates high correlation between predictors.[13] In addition, a sensitivity analysis was performed after excluding from the model the variables with the highest scores in the similarity matrix obtained by the use of a specific function for identifying collinear predictors (varclus).[14] The statistical software package R version 2.15.1 (*R Foundation for Statistical Computing, Vienna, Austria*) was used for analyses.

Results

A total of 10 004 patients with 15 004 treated lesions met the enrolment criteria and had routine control angiography at 6- to 8-month follow-up. The main characteristics of patients ($n = 2900$) who did not receive angiographic surveillance have been previously reported:[1] briefly, these patients were older (age 68.9 $\pm$ 10.9 vs. 65.4 $\pm$ 12.3 years, $P < 0.001$), more likely diabetics (30.8 vs. 24.0%, $P < 0.001$) and with a similar proportion of DES implanted (54.3 vs. 53.5%, $P = 0.47$) in comparison with patients with invasive surveillance. At the time of index PCI, BMS was used in 4649 patients and DES in 5355 patients. Overall, routine control angiography was performed at a median of 198.5 days (182.0; 216.2) after the index intervention. Angiographic restenosis was detected in 2643 (26.4%) patients with 3098 treated lesions and a diameter stenosis of 68.6 $\pm$ 15.8%. The restenosis morphology was as follows: 34% focal body, 15% focal margin, 5% multifocal, 38% diffuse, 2% proliferative, and 5% occlusive. Baseline characteristics of patients with and without restenosis have previously been reported[1] and are shown in Supplementary material online, *Table S1* and *S2*. Overall, TVR was performed in 1724 (65.2%) patients among those presenting with restenosis at surveillance angiography: TVR was successful in 98.0% of patients with a final diameter stenosis of 15.5 $\pm$ 12.0%.

Restenosis and 4-year mortality

There were 702 deaths during the 4-year follow-up: 218 deaths occurred among patients with restenosis and 484 deaths occurred among patients without restenosis [Kaplan–Meier estimates of

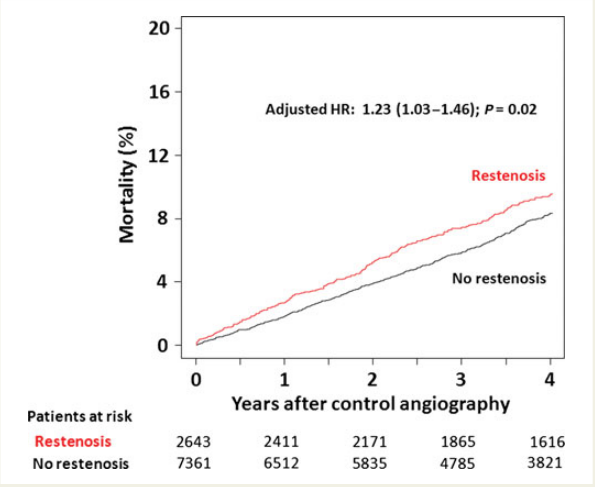

Figure 1 Kaplan–Meier curves of 4-year mortality according to the presence of restenosis at routine control angiography. HR, hazard ratio.

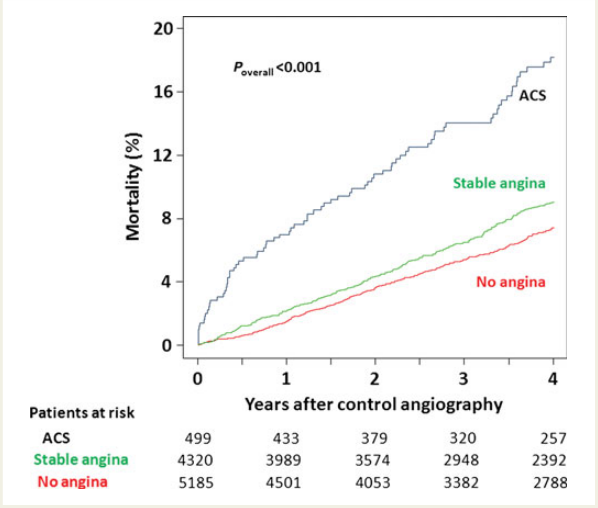

Figure 2 Kaplan–Meier curves of 4-year mortality according to clinical presentation at routine control angiography. ACS, acute coronary syndrome.

4-year-mortality 9.6 and 8.3%, respectively, HR 1.19; (95% CI: 1.02–1.40); $P = 0.03$, *Figure 1*]. Among patients with restenosis at control angiography, the decision to perform a TVR did not impact the 4-year-mortality risk: a total of 151 deaths occurred among patients with TVR and 67 deaths occurred among patients without TVR [Kaplan–Meier estimates of 4-year mortality 9.0 and 10.0%, respectively, HR: 1.12; (95% CI: 0.84–1.49); $P = 0.43$].

The variables to be entered into the multivariable model showed a VIF between 1.02 and 1.29, excluding any concerning multicollinearity. According to the multivariable Cox proportional hazards model, the presence of restenosis at routine control angiography [HR: 1.23; (95% CI: 1.03–1.46); $P = 0.02$], age [for each 10-year increase, HR: 2.34; (95% CI: 2.12–2.60); $P < 0.001$], diabetes mellitus [HR: 1.68; (95% CI: 1.41–1.99); $P < 0.001$], current smoking habit [HR 1.39; (95% CI: 1.09–1.76); $P = 0.01$], and left ventricular ejection fraction [for each 5% decrease, HR: 1.39; (95% CI: 1.31–1.48); $P < 0.001$] was independently associated with higher likelihood of death after 4 years. Female gender [HR: 0.73; (95% CI: 0.60–0.88); $P < 0.001$] was independently associated with lower likelihood of death after 4 years. In an additional sensitivity analysis, the multivariable model was reapplied after excluding three variables that showed the highest scores in the similarity matrix: arterial hypertension, current smoking habit, and multivessel disease. This analysis reconfirmed the significant predictive role of restenosis at routine control angiography [HR: 1.23; (95% CI: 1.04–1.47); $P = 0.018$]. An additional multivariable Cox proportional hazards model included lesion-based variables highly predictive of restenosis (vessel diameter, stented length, complex lesion):[1] in this model the presence of restenosis at routine control angiography remained independently associated with higher likelihood of death after 4 years [HR: 1.35; (95% CI: 1.02–1.80); $P = 0.03$].

Clinical presentation at control angiography and 4-year mortality

At the time of follow-up angiography, 499 patients (5.0%) presented with an acute coronary syndrome, 4320 patients (43.2%) complained of stable angina pectoris, while 5185 patients (51.8%) were asymptomatic. Patients presenting with acute coronary syndrome showed up at a shorter interval for follow-up angiography after the index PCI [a median of 170.0 days (111.9; 222.4)] when compared with both patients complaining of stable angina [a median of 199.1 days (185.7; 214.6)] and asymptomatic patients [a median of 198.7 days (175.7; 217.9), $P < 0.001$]. Patients with acute coronary syndrome had the highest 4-year-mortality risk (overall $P < 0.001$, *Figure 2*).

Restenosis in asymptomatic patients and 4-year mortality

Among the group of 5185 asymptomatic patients, a total of 955 (18.4%) had restenosis: of these, 389 patients (40.7%) underwent TVR. The severity of restenosis was higher among those patients treated by TVR (diameter stenosis 60.4 ± 22.8 vs. 53.4 ± 24.0% in those without TVR, $P < 0.001$). To shed more light on the prognostic role of restenosis in those patients presenting without angina at the time of follow-up angiography, additional analysis was done. There were 300 deaths among asymptomatic patients during the 4-year follow-up: 73 deaths occurred among patients with restenosis and 227 deaths occurred among patients without restenosis [Kaplan–Meier estimates of 4-year mortality 9.2 and 7.0%, respectively, HR 1.36; (95% CI: 1.05–1.77); $P = 0.02$, *Figure 3*]. According to the multivariable Cox proportional hazards model, the presence of restenosis at routine control angiography [HR: 1.40; (95% CI: 1.06–1.87); $P = 0.01$], age [for each 10-year increase, HR: 2.26; (95% CI: 1.93–2.64); $P < 0.001$], diabetes mellitus [HR: 1.86; (95% CI: 1.43–2.41); $P < 0.001$], and left ventricular ejection fraction [for each 5% decrease, HR: 1.44; (95% CI: 1.32–1.57); $P < 0.001$] was independently associated with higher likelihood of death after 4 years. Female gender [HR: 0.72; (95% CI: 0.53–0.97); $P = 0.03$] was independently associated with lower likelihood of death after 4 years. In an additional sensitivity analysis, the multivariable model without arterial

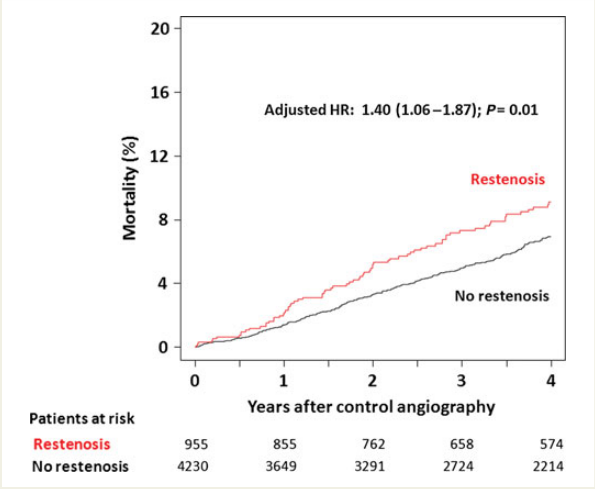

Figure 3 Kaplan–Meier curves of 4-year mortality according to the presence of restenosis at routine control angiography among asymptomatic patients. HR, hazard ratio.

hypertension, current smoking habit, and multivessel disease, showing the highest scores in the similarity matrix, reconfirmed the significant predictive role of restenosis at routine control angiography [HR: 1.41; (95% CI: 1.06–1.87); $P = 0.019$].

Discussion

In the current analysis, we reported the 4-year-mortality risk of patients with or without restenosis in 10 004 patients undergoing routine control angiography after coronary stenting at two centres in Germany. The main findings are (i) the presence of restenosis predicts an increased risk of 4-year mortality; (ii) restenosis provides prognostic information that is independent of that provided by other relevant clinical factors; and (iii) the prognostic value associated with restenosis is maintained even if patients present without symptoms at time of follow-up angiography.

Angiographic restenosis is usually defined as a binary measure being adjudicated in the presence of ≥50% lumen diameter stenosis at surveillance angiography performed typically 6–9 months after PCI.[15–17] The introduction of DES significantly lowered both clinical and angiographic restenosis when compared with BMS.[1,18] The improved efficacy associated with DES was a pre-requisite for the expansion of percutaneous intervention to increasingly complex subsets.[19] However, as rates of restenosis increase with disease complexity, the relationship between restenosis and long-term mortality represents an issue of broad clinical importance.

A routine control angiography represents the best method for detecting restenosis, providing valid estimates of the relative efficacy of different devices.[2] Notwithstanding this, whether knowledge of the patency status of the coronary tree at a time point following PCI might be of relevance to all patients treated with stents remains a matter of ongoing controversy.

On the one side, in a previous study, evidence of restenosis at routine control angiography increased the risk of long-term mortality as a straightforward function of the degree of angiographic restenosis.[12] On the other side, a number of observations in relatively small PCI-cohorts treated with BMS[20] or DES[7,8,21,22] failed to support a strategy of routine control angiography after stenting mainly because they focused on the value of routine control angiography *per se* rather than on the prognostic relevance of restenosis. On the one hand a control angiography is merely a diagnostic procedure providing no further information other than defining the actual luminal calibre of the vessel at follow-up after stent implantation. Against this, however, restenosis at the site of intervention represents a potentially valuable surrogate marker for clinical outcomes.[2,23]

The present study assessed the prognostic relevance of restenosis in the largest unrestricted population undergoing coronary stenting and routine control angiography since the introduction of percutaneous intervention. We focused on angiographically proved restenosis as this likely represents the most objective parameter of efficacy after stent implantation.[24] Restenosis was independent predictor of higher mortality after 4-year follow-up together with other relevant clinical factors including age, sex, diabetes mellitus, smoke habit, previous by-pass surgery, and left ventricular ejection fraction. The prognostic role of restenosis was confirmed not just in the overall cohort but also in those patients undergoing routine control angiography without anginal symptoms.

It is well recognized that routine angiographic surveillance after PCI leads to higher rates of repeat intervention, without clear advantages when compared with a surveillance strategy in which repeat angiography is reserved for the evaluation of recurrent symptoms or objective signs of myocardial ischaemia.[7,8] In line with this, outside the setting of clinical trials, recommendations for control angiography after PCI are restricted to those patients with recurrent symptoms or signs of ischaemia.[9] Against this background, the findings of the current analysis are notable, showing that stable patients presenting asymptomatic restenosis at routine control angiography have a higher risk of death at 4-year follow-up in comparison with those without restenosis. In other words, in patients treated with stents the presence of asymptomatic restenosis detected at routine control angiography provides additional clinically relevant information concerning long-term mortality risk. However, the present study does not indicate that routine control angiography *per se* is a predictor of long-term mortality. Indeed, the understanding of a potential role for routine angiographic surveillance for risk stratification in PCI-treated patients, as well as of a prognostic role of reintervention in patients presenting asymptomatic restenosis is beyond the scope of this study. Both these questions can be ascertained only in the context of a properly designed randomized trial including non-invasive assessment of ischaemic burden, integrating new intravascular imaging modalities and functional flow assessment in the treatment decision process for restenosis and dissecting causes of angina at control-angiography other than stenoses of epicardial vessels (i.e. microvascular disease, functional vascular disease).

In the current analysis, the survival curves for patients with and without restenosis appear to diverge soon after at follow-up angiography. This aspect merits careful discussion. Higher rate of repeat revascularization is recognized to be the principal trade-off of routine control angiography and it is important to exclude the potential adverse impact of repeat revascularization in patients presenting angiographic restenosis. In line with this we calculated 4-year

mortality risk for those patients presenting with restenosis at routine control angiography according to the management received (conservative vs. repeat revascularization) and found no difference according to the strategy selected. This speaks against a negative influence of repeat revascularization at the time of control angiography on subsequent mortality risk out to 4 years.

Study limitations

The current study has some limitations. First, we were unable to investigate the possible causative effect of restenosis on mortality risk. Second, data regarding non-cardiac co-morbidities and concomitant medications throughout the follow-up period are limited and possible bias due to incomplete information is possible. Third, we did not routinely assess ischaemic burden in patients undergoing control angiography. However, recent evidence suggests that anatomic burden derived from quantitative angiographic assessment of coronary disease but not ischaemic burden is predictive of adverse outcomes in patients suitable for revascularization.[25] Fourth, we neither had data on anginal status after index PCI nor on whether angina at time of control angiography was due to cardiovascular diseases other than stenoses of the epicardial vessels. Finally, although we carefully documented and analysed the anginal status at the time of follow-up angiography, the immediate impact of index PCI on anginal symptoms was not formally assessed nor was fully excluded that other cardiovascular diseases not related to the epicardial coronary vessels were at the origin of anginal symptoms. The integration of new intravascular imaging modalities and functional flow assessment in the treatment decision process for restenosis may enhance our ability to mitigate the risk associated with this finding.

Conclusions

Evidence of restenosis after coronary stent implantation was predictive of 4-year mortality in this large cohort of patients with angiographic surveillance after coronary stenting even in patients that were asymptomatic. The evidence of restenosis provided prognostic information complementary to that provided by other relevant clinical characteristics including age, sex, diabetes mellitus, smoking habit, previous by-pass surgery, and left ventricular ejection fraction. These findings provide a basis for suggesting that newer-generation drug-eluting stents may have a meaningful impact on long-term mortality through the reduction in restenosis after coronary stenting. Whether routine control angiography after coronary stenting is beneficial and influences outcomes should be evaluated by properly designed randomized trials.

Supplementary material

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

Conflict of interest: R.A.B. received lecture fees from B. Braun and Biotronik. A.K. has submitted patents in relation to a number of DES technologies and received consulting or lecture fees from Abbott, Biosensors and Biotronik. The other authors declare no potential conflict of interest.

Authors' contributions

S.C. and A.K. conceived and designed the study. A.K. supervised the conduct of the trial and data collection. S.C. and A.K. provided statistical advice on study design and analysed the data. S.C., A.K., and R.A.B. wrote the paper; S.S., P.H., J.K., A.F., T.I., I.O., M.F., K.-L.L., H.S. contributed substantially to its revision. S.C. and A.K. take responsibility for the paper as a whole. S.C., R.A.B., K.-L.L., H.S., and A.K. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All the authors approved the manuscript.

References

1. Cassese S, Byrne RA, Tada T, Pinieck S, Joner M, Ibrahim T, King LA, Fusaro M, Laugwitz KL, Kastrati A. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart* 2014;**100**:153–159.
2. Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol* 2014;**63**:2659–2673.
3. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. *Circulation* 2005;**111**:3435–3442.
4. Pocock SJ, Lansky AJ, Mehran R, Popma JJ, Fahy MP, Na Y, Dangas G, Moses JW, Pucelikova T, Kandzari DE, Ellis SG, Leon MB, Stone GW. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol* 2008;**51**:23–32.
5. Byrne RA, Eberle S, Kastrati A, Dibra A, Ndrepepa G, Iijima R, Mehilli J, Schomig A. Distribution of angiographic measures of restenosis after drug-eluting stent implantation. *Heart* 2009;**95**:1572–1578.
6. Brener SJ, Prasad AJ, Khan Z, Sacchi TJ. The relationship between late lumen loss and restenosis among various drug-eluting stents: a systematic review and meta-regression analysis of randomized clinical trials. *Atherosclerosis* 2011;**214**:158–162.
7. Uchida T, Popma J, Stone GW, Ellis SG, Turco MA, Ormiston JA, Muramatsu T, Nakamura M, Nanto S, Yokoi H, Baim DS. The clinical impact of routine angiographic follow-up in randomized trials of drug-eluting stents: a critical assessment of 'oculostenotic' reintervention in patients with intermediate lesions. *JACC Cardiovasc Interv* 2010;**3**:403–411.
8. Stone GW, Parise H, Witzenbichler B, Kirtane A, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Mockel M, Lansky AJ, Mehran R. Selection criteria for drug-eluting versus bare-metal stents and the impact of routine angiographic follow-up: 2-year insights from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. *J Am Coll Cardiol* 2010;**56**:1597–1604.
9. Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS, Dehmer GJ, Kirtane AJ, Wann LS, Ward RP. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;**59**:1995–2027.
10. Weintraub WS, Ghazzal ZM, Douglas JS Jr, Morris DC, King SB III. Usefulness of the substitution of nonangiographic end points (death, acute myocardial infarction, coronary bypass and/or repeat angioplasty) for follow-up coronary angiography in evaluating the success of coronary angioplasty in patients with angina pectoris. *Am J Cardiol* 1998;**81**:382–386.
11. Rupprecht HJ, Espinola-Klein C, Erbel R, Nafe B, Brennecke R, Dietz U, Meyer J. Impact of routine angiographic follow-up after angioplasty. *Am Heart J* 1998;**136**(4 Pt 1):613–619.
12. Schuhlen H, Kastrati A, Mehilli J, Hausleiter J, Pache J, Dirschinger J, Schomig A. Restenosis detected by routine angiographic follow-up and late mortality after coronary stent placement. *Am Heart J* 2004;**147**:317–322.
13. Heiberger RM. HH: Statistical Analysis and Data Display: Heiberger and Holland, 2013. **http://CRAN.R-project.org/package=HH**.
14. Harrell FE Jr, Dupont C. Harrell Miscellaneous, 2012. **http://CRAN.R-project.org/package=Hmisc**.

15. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous Flow Response and Regional Distribution During Coronary Hyperemia as Measures of Coronary Flow Reserve. *Am J Cardiol* 1974;**33**:87–94.
16. Kuntz RE, Baim DS. Defining coronary restenosis. Newer Clinical and Angiographic Paradigms. *Circulation* 1993;**88**:1310–1323.
17. Eeckhout E, Serruys PW, Wijns W, Vahanian A, Van Sambeek M. In: *Percutaneous Interventional Cardiovascular Medicine: the PCR - EAPCI Textbook*. Europa Ed.; 2012 p. 785–826.
18. Bangalore S, Toklu B, Amoroso N, Fusaro M, Kumar S, Hannan EL, Faxon DP, Feit F. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ* 2013;**347**:f6625.
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. Ruygrok PN, Melkert R, Morel MA, Ormiston JA, Bar FW, Fernandez-Aviles F, Suryapranata H, Dawkins KD, Hanet C, Serruys PW. Does angiography six months after coronary intervention influence management and outcome? Benestent II Investigators. *J Am Coll Cardiol* 1999;**34**:1507–1511.
21. Lansky AJ, Brar SS, Yaqub M, Sood P, Applegate RJ, Lazar D, Jankovic I, Hermiller JB, Koo K, Sudhir K, Stone GW. Impact of routine angiographic follow-up after percutaneous coronary intervention with drug-eluting stents in the SPIRIT III randomized trial at three years. *Am J Cardiol* 2012;**110**:21–29.
22. Pinto DS, Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Mehran R, Na Y, Turco M, Caputo R, Popma JJ, Cutlip DE, Russell ME, Cohen DJ, Investigators T-I. Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents: results from the TAXUS-IV trial. *J Am Coll Cardiol* 2006; **48**:32–36.
23. Park SJ, Kang SJ, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. *J Am Coll Cardiol* 2012;**59**: 2051–2057.
24. Mauri L, Orav EJ, Candia SC, Cutlip DE, Kuntz RE. Robustness of late lumen loss in discriminating drug-eluting stents across variable observational and randomized trials. *Circulation* 2005;**112**:2833–2839.
25. Mancini GB, Hartigan PM, Shaw LJ, Berman DS, Hayes SW, Bates ER, Maron DJ, Teo K, Sedlis SP, Chaitman BR, Weintraub WS, Spertus JA, Kostuk WJ, Dada M, Booth DC, Boden WE. Predicting outcome in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation): coronary anatomy versus ischemia. *JACC Cardiovasc Interv* 2014;**7**:195–201.