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Original article

Incidence and Predictors of reCurrent Restenosis After Drug-coated Balloon Angioplasty for Restenosis of a drUg-eluting Stent: The ICARUS Cooperation

Salvatore Cassese,[a,*] Bo Xu,[b] Seiji Habara,[c] Harald Rittger,[d] Robert A. Byrne,[a] Matthias Waliszewski,[e] María José Pérez-Vizcayno,[f] Runlin Gao,[b] Adnan Kastrati,[a,g] and Fernando Alfonso[h]

[a] *Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München, Technische Universität München, München, Germany*
[b] *National Center for Cardiovascular Diseases, Fu Wai Hospital, Beijing, China*
[c] *Department of Cardiology, Kurashiki Central Hospital, Okayama, Japan*
[d] *Medizinische Klinik I, Klinikum Fürth, Fürth, Germany*
[e] *Medical Scientific Affairs, B. Braun Vascular Systems, Berlin, Germany*
[f] *Fundación Interhospitalaria de Investigación Cardiovascular, Hospital Universitario Clínico San Carlos, Madrid, Spain*
[g] *German Centre for Cardiovascular Research (Deutsche Zentrum für Herz-Kreislauf-Forschung, DZHK), partner site Munich Heart Alliance, München, Germany*
[h] *Servicio de Cardiología, Hospital Universitario de La Princesa, Madrid, Spain*

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ABSTRACT

Introduction and objectives: The incidence and predictors of recurrent restenosis after drug-coated balloon (DCB) angioplasty for drug-eluting stent (DES) restenosis remain poorly studied. We sought to evaluate the incidence and predictors of recurrent restenosis among participants in randomized controlled trials receiving DCB angioplasty for DES restenosis.

Methods: The clinical and lesion data of individuals enrolled in 6 randomized controlled trials of DCB angioplasty for DES restenosis were pooled. All patients included in this report were assigned to receive paclitaxel-coated balloon angioplasty with the SeQuent Please DCB (B Braun, Melsungen, Germany). The current analysis focused on participants with available follow-up angiography at 6 to 9 months. The incidence of recurrent restenosis, defined as diameter restenosis $\geq$ 50% in the in-segment area at follow-up angiography, and its clinical and angiographic predictors were evaluated.

Results: A total of 546 patients were combined in a single dataset. Angiographic follow-up at 6 to 9 months was available for 484 patients (88.6%) with 518 treated lesions. Recurrent restenosis was detected in 101 (20.8%) patients. On multivariable analysis, lesion length (OR, 1.58; 95%CI, 1.10-2.26; P = .012 for 5 mm increase) and vessel size (OR, 1.42; 95%, 1.12-1.79; P = .003 for 0.5 mm reduction) were independently associated with recurrent restenosis.

Conclusions: In the largest cohort to date of individuals with angiographic surveillance after DCB angioplasty for DES restenosis, we demonstrated that recurrent restenosis occurs in approximately 1 out of 5 patients. Predictors of recurrent restenosis are increased lesion length and small vessel size.

Incidencia y predictores de la reestenosis recurrente tras angioplastia con balón farmacoactivo en reestenosis de *stents* farmacoactivos: proyecto cooperativo ICARUS

Palabras clave:
Angiografía
Enfermedad coronaria
Balón farmacoactivo
Stent farmacoactivo
Reestenosis

RESUMEN

Introducción y objetivos: No se ha estudiado bien la incidencia y los predictores de la reestenosis recurrente tras angioplastia con balón farmacoactivo (BFA) en reestenosis de *stents* farmacoactivos (SFA). Nuestro objetivo es analizar la incidencia y los predictores de la reestenosis recurrente en los estudios aleatorizados en que se utilizaron BFA para el tratamiento de la reestenosis del SFA.

Métodos: Los datos clínicos y anatómicos de los pacientes incluidos en 6 estudios aleatorizados sobre BFA para el tratamiento de reestenosis de SFA se analizaron en conjunto. Se asignó a todos los pacientes incluidos en este análisis a tratamiento con el BFA de paclitaxel SeQuent Please (B Braun; Melsungen, Alemania). El análisis se centró en los pacientes que tenían seguimiento angiográfico a los 6-9 meses. Se evaluó tanto la incidencia de reestenosis (definida como estenosis $\geq$ 50% del diámetro luminal en el análisis por segmento durante el seguimiento angiográfico tardío) como sus predictores clínicos y angiográficos.

* Corresponding author: Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse 36, 80636 München, Germany.
E-mail address: cassese@dhm.mhn.de (S. Cassese).

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Resultados: Los datos de 546 pacientes se incluyeron en una única base de datos. De 484 pacientes (88,6%), con un total de 518 lesiones tratadas, se disponía de seguimiento angiográfico tardío, y se detectó recurrencia de reestenosis en 101 pacientes (20,8%). En el análisis multivariable, la longitud de la lesión (por cada incremento de 5 mm, OR = 1,58; IC95%, 1,10-2,26; p = 0,012) y el tamaño del vaso (por cada reducción de 0,5 mm, OR = 1,42; IC95%, 1,12-1,79; p = 0,003) se asociaron de manera independiente con la recurrencia de reestenosis.

Conclusiones: Este estudio, el mayor disponible de pacientes tratados con BFA por reestenosis de SFA con seguimiento angiográfico tardío, demuestra que la recurrencia de reestenosis se produce en 1 de cada 5 de estos pacientes. Los predictores de la reestenosis recurrente son la longitud de la lesión y el tamaño del vaso.

Abbreviations

DCB: drug-coated balloon
DES: drug-eluting stent

INTRODUCTION

Contemporary drug-eluting stents (DES) have markedly reduced the need for reintervention compared with both bare metal stents and early-generation DES. However, the occurrence of restenosis due to neointimal proliferation and/or neoatherosclerosis within stented segments is still the main reason for DES failure.[1] Moreover, the optimal treatment of DES restenosis remains a matter of debate and continues to be associated with high rates of recurrent restenosis.[2]

In patients with DES restenosis, European guidelines recommend treatment with either drug-coated balloon (DCB) or repeat stenting with DES; recommendations for both options are supported by a similar level of evidence.[3] Drug-coated balloon represents an attractive treatment option, providing antiproliferative efficacy without the requirement for an additional stent implant.[4] Although recent studies of patients with DES restenosis ranked the antirestenotic potency of DCB as the second most effective treatment after repeat stenting with everolimus-eluting stents,[5] this treatment might be the preferred option for patients due to concerns about the late outcomes of patients treated with multiple stent layers.[6]

Follow-up angiography is the modality of choice for the detection of lumen renarrowing after coronary intervention and for assessment of device efficacy.[7] To date, however, investigations of the incidence and predictors of recurrent restenosis after DCB angioplasty for DES restenosis remain scarce. Moreover, the identification of clinical, angiographic and procedural risk factors predicting the risk of recurrent restenosis at follow-up angiography may provide a basis for treatment optimization or individualization of revascularization strategies in specific patient and lesion subsets. In this report, we evaluated the incidence and predictors of recurrent restenosis in a cohort of patients treated with DCB angioplasty for DES restenosis in the setting of randomized controlled trials.

METHODS

Data Sources and Eligibility Criteria

For inclusion in the current analysis, randomized trials of DCB therapy for patients with stable or unstable coronary artery disease because of DES restenosis were identified by searching Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the abstracts of scientific sessions, and relevant websites. No restrictions in terms of language or publication status were imposed. The reference lists from all eligible studies and previous meta-analyses on this topic[5,8] were checked to identify further citations. Search terms included the keywords and the corresponding Medical Subject Headings for "drug-coated (-eluting) balloon", "paclitaxel-coated (-eluting) balloon", "drug-eluting stent(s)", "restenosis", "trial", and "randomized trial". Inclusion criteria consisted of randomized design and the availability of follow-up angiography data 6 to 9 months after the index procedure. Investigations of DCB angioplasty for indications other than DES restenosis were ineligible. The last search was performed on June 22, 2016.

Collection of Individual Participant Data and Quality Assessment

Two investigators (S. Cassese and R.A. Byrne) independently assessed publications for eligibility at the title and/or abstract level. Divergences were resolved by consensus. Studies that met the inclusion criteria were selected for further analysis. Freedom from bias was evaluated for each study in accordance with The Cochrane Collaboration method.[9] Composite quality scores were not assigned.[10]

Of 8 studies identified through the electronic search, 2 randomized trials[11] were excluded since the overall percentage of patients receiving DCB angioplasty because of DES restenosis was $< 5\%$. Finally, 6 randomized trials[12–17] were available for inclusion in the present analysis. The principal investigators of these studies were contacted to provide individual data of participants randomly assigned to DCB angioplasty. Data was transferred without patient identifiers to the *ISAResearch Center* (*Deutsches Herzzentrum München, Technische Universität München*, Munich, Germany) and combined in a single pooled database. The final dataset was checked for completeness and consistency and compared with the results of prior publications. Principal investigators were directly contacted in case of requirement for additional data. Data were analyzed according to the intention-to-treat principle. Each study included in the present analysis was approved by the institutional review board or ethics committee at each participating center, and all patients provided informed, written consent before receiving the assigned treatment.

Angiographic Data and Study Definitions

At baseline, procedural parameters were gathered and follow-up coronary angiograms were digitally recorded and assessed off-line with automated edge-detection systems by independent operators in all studies.[12–17] Lesion characteristics were described in accordance with standard definitions, while restenosis morphology was classified according to criteria modified from Mehran et al.[18]

The angiographic and procedural parameters collected for the current analysis were vessel size, lesion length, initial diameter stenosis, maximal balloon pressure, final lumen diameter, and final

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