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# Colchicine Treatment for the Prevention of Bare-Metal Stent Restenosis in Diabetic Patients

Spyridon Deftereos, MD,* Georgios Giannopoulos, MD,*† Konstantinos Raisakis, MD,* Charalambos Kossyvakis, MD,* Andreas Kaoukis, MD,* Vasiliki Panagopoulou, MD,* Metaxia Driva, MD,* George Hahalis, MD,‡ Vlasios Pyrgakis, MD,* Dimitrios Alexopoulos, MD,‡ Antonis S. Manolis, MD,§ Christodoulos Stefanadis, MD,‖ Michael W. Cleman, MD†

*Athens and Patras, Greece; and New Haven, Connecticut*

**Objectives** This study sought to test the hypothesis that colchicine treatment after percutaneous coronary intervention (PCI) can lead to a decrease in in-stent restenosis (ISR).

**Background** ISR rates are particularly high in certain patient subsets, including diabetic patients, especially when a bare-metal stent (BMS) is used. Pharmacological interventions to decrease ISR could be of clinical relevance.

**Methods** Diabetic patients with contraindication to a drug-eluting stent, undergoing PCI with a BMS, were randomized to receive colchicine 0.5 mg twice daily or placebo for 6 months. Restenosis and neointima formation were studied with angiography and intravascular ultrasound 6 months after the index PCI.

**Results** A total of 196 patients (63.6 ± 7.0 years of age, 128 male) were available for analysis. The angiographic ISR rate was 16% in the colchicine group and 33% in the control group ($p = 0.007$; odds ratio: 0.38, 95% confidence interval: 0.18 to 0.79). The number needed to treat to avoid 1 case of angiographic ISR was 6 (95% confidence interval: 3.4 to 18.7). The results were similar for IVUS-defined ISR (odds ratio: 0.42; 95% confidence interval: 0.22 to 0.81; number needed to treat = 5). Lumen area loss was 1.6 $mm^2$ (interquartile range: 1.0 to 2.9 $mm^2$) in colchicine-treated patients and 2.9 $mm^2$ (interquartile range: 1.4 to 4.8 $mm^2$) in the control group ($p = 0.002$). Treatment-related adverse events were largely limited to gastrointestinal symptoms.

**Conclusions** Colchicine is associated with less neointimal hyperplasia and a decreased ISR rate when administered to diabetic patients after PCI with a BMS. This observation may prove useful in patients undergoing PCI in whom implantation of a drug-eluting stent is contraindicated or undesirable. (J Am Coll Cardiol 2013;61:1679–85)


Implantation of coronary stents after angioplasty has led to significant decreases in clinical events compared with plain balloon angioplasty (1,2). However, restenosis has been a considerable problem with bare-metal stents (BMS), which prompted the advent of drug-eluting stents. Their principal function is to inhibit in-stent neointima formation, thus decreasing restenosis rates (3).

The problem of restenosis appears to be more severe in certain subsets of coronary artery disease patients, including those with diabetes, in whom some of the first BMS trials restenosis rates exceeded 50% (4). As a result, drug-eluting stents are particularly beneficial in these patients, in terms of angiographic outcomes and target lesion revascularization (5). However, there are diabetic patients undergoing percutaneous coronary intervention (PCI) who have important contraindications to implantation of drug-eluting stents, including patients with planned necessary surgery as well as those who need anticoagulation treatment, in whom triple antithrombotic therapy (double antiplatelet and 1 anticoagulant) is associated with a high risk of bleeding and should be as short term as possible (6).

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Colchicine is an old drug with known anti-inflammatory and antiproliferative actions. Both of these effects could conceivably interfere with the formation of neointima in coronary stents, thus reducing the rate of in-stent restenosis

From the *Department of Cardiology, Athens General Hospital "G. Gennimatas," Athens, Greece; †Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut; ‡Department of Cardiology, University of Patras Medical School, Patras, Greece; §1st Department of Cardiology, Evaggelismos General Hospital, Athens, Greece; and the ‖1st Department of Cardiology, University of Athens Medical School, Athens, Greece. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Deftereos and Giannopoulos contributed equally to this paper.

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**Abbreviations and Acronyms**

angio-ISR = angiographic in-stent restenosis

BMS = bare-metal stent(s)

CI = confidence interval

ISR = in-stent restenosis

IVUS = intravascular ultrasound

IVUS-ISR = intravascular ultrasound-defined in-stent restenosis rate

MLA = minimum lumen area

PCI = percutaneous coronary intervention

(ISR). In addition, it has been shown to be safe in different subsets of patients with cardiovascular disease (7,8). The aim of the present study was to study the effect of 6 months of treatment with oral colchicine on neointima formation and restenosis in diabetic patients undergoing PCI with BMS implantation.

## Methods

**Population.** This was a double-blind, prospective, placebo-controlled study. Eligible patients were diabetic, 40 to 80 years of age, undergoing PCI in a coronary artery with a diameter of at least 2.5 mm with a BMS. Acceptable reasons for not implanting a drug-eluting stent were: contraindication to long-term dual antiplatelet treatment, need for triple antithrombotic therapy, planned or high probability of necessary surgery in the following 12 months, or the patient's expressed wish in the context of the PCI informed consent procedure. Only 1 lesion per patient was included in the study. (If PCI was performed in >1 coronary site in a patient, the site with the greater artery diameter was included.) Diabetes mellitus had to be previously diagnosed by a specialist, with the patient treated with either oral medication or insulin. Exclusion criteria were left main artery disease (>30% in angiography); PCI performed as primary treatment for ST-segment elevation myocardial infarction, hepatic impairment (Child-Pugh class B or C); target vessel segment presenting particular technical challenges for intravascular ultrasound (IVUS) (e.g., marked tortuosity, vessel with steep take-off angle); severe or end-stage renal failure (estimated glomerular filtration rate ≤20 ml/min/1.73 $m^2$ or requiring dialysis); history of intolerance to colchicine, myopathy, and statin hepatotoxicity or myotoxicity; women with child-bearing potential; and inability or unwillingness to adhere to standard treatment or to provide consent. The protocol was approved by the institutional review boards. All patients provided informed consent.

**Procedures.** Patients underwent baseline coronary angiography and PCI, with IVUS evaluation of the implanted BMS. All stents were post-dilated with an appropriately sized noncompliant balloon. All stents were evaluated immediately after implantation with IVUS to obtain baseline measurements. Immediate post-implantation IVUS images were also used to optimize stent expansion and apposition and to identify significant edge dissections or significant residual plaque burden at stent edges, whereupon complementary corrective action was undertaken (e.g., further post-dilation or additional stenting), if deemed appropriate by the operator. (It was determined by the review board who approved of the study protocol that it would not be ethical to disregard IVUS findings, although routine post-PCI IVUS-guided stent evaluation does not reflect current clinical practice.) Angiographic and IVUS follow-up was performed 6 months after the index PCI.

Angiographic vessel and lesion parameters were measured using quantitative coronary angiography software (Xcelera, Philips Healthcare, Eindhoven, the Netherlands). Late lumen loss was defined as the difference between the baseline in-stent minimum luminal diameter and the minimum luminal diameter on follow-up angiography. Angiographic ISR (angio-ISR) was defined as presence of >50% in-stent stenosis at the 6-month follow-up.

IVUS was performed after intracoronary administration of 0.3 to 0.5 mg of nitroglycerin. A digital IVUS catheter (Eagle Eye Gold, Volcano Corp., Rancho Cordova, California) was introduced into the target vessel and a pull back was performed through the implanted stent, with a motorized automatic pull back system (Track Back II, Volcano Corp.) at a constant speed of 0.5 mm/s. Additional pull backs were performed to ensure adequate quality of captured images. Captured IVUS data, identified only by a serial number, were analyzed offline. Each recorded pull back loop was inspected by formally trained IVUS operators who made manual corrections to the automated border delineation applied by the system software. Volumetric data were then automatically calculated. Neointima volume was calculated as stent minus lumen volume and divided by the stent length in millimeters to account for different stent lengths (normalized neointima volume). The percentage of neointimal volume was defined as in-stent neointimal volume divided by stent volume. In-stent minimum lumen area (MLA) was measured and recorded. IVUS-defined ISR (IVUS-ISR) was defined as in-stent MLA of <4 $mm^2$ at follow-up (a cutoff used in past studies [9]). In-stent lumen area loss was calculated as post-PCI MLA minus the MLA at follow-up. A subset of the pull backs (~20%) were analyzed twice, unbeknown to the reviewers. The intraobserver correlation index was 0.93 for lumen measurements and 0.91 for volumes. All IVUS pull backs were analyzed at a core laboratory.

**Study treatments and adverse event monitoring.** Patients were randomized to receive colchicine or placebo for 6 months. Colchicine was administered from the day of the index PCI (within 24 h) at a dose of 0.5 mg twice daily. Patients were followed with clinic visits until follow-up angiography at 6 months. Monitoring of adverse events focused on gastrointestinal manifestations, hepatotoxicity, myelotoxicity/hematotoxicity, myotoxicity, and alopecia. Complete blood counts and standard biochemical analyses (glucose, urea, creatinine, liver enzymes, creatine kinase, lactate dehydrogenase) were performed at 2, 4, 8, 16, and 24 weeks after the index PCI.

**Outcome measures.** The main outcome measures were angio-ISR and IVUS-ISR. Secondary outcome measures were angiographic and IVUS parameters of lumen loss and