

## Editorial

## Dynamic Nature of Coronary Plaques and Clinical Outcomes in Diabetic Patients: Is Change in Itself Bad?

## Naturaleza dinámica de las placas coronarias y resultados clínicos en pacientes diabéticos: ¿es malo el cambio de por sí?

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Atherothrombotic cardiovascular events are related not only to luminal stenosis severity but also to plaque composition. This has led to the concept of *vulnerable* plaque, referring to those lesions more likely to rupture and cause clinical syndromes. Features of vulnerability include large necrotic core, thin fibrous cap, or active inflammation, amongst others.<sup>1</sup> Diabetes mellitus, through a variety of mechanisms, is a well known risk factor for increased cardiovascular risk.<sup>2,3</sup> Prior studies using serial intravascular ultrasound (IVUS) to assess coronary atherosclerosis have demonstrated an association between the presence of diabetes and not only increased plaque burden but also faster plaque progression and inadequate constrictive remodeling.<sup>4</sup> Moreover, when studied with IVUS virtual histology, diabetic patients have larger necrotic cores and higher prevalence of isolated or multiple thin-cap fibroatheromas.<sup>5,6</sup>

In the article published in *Revista Española de Cardiología*, Jiménez-Quevedo et al.<sup>7</sup> describe the plaque changes in 45 type 2 diabetic patients with established coronary artery disease enrolled in 3 prospective stent trials, who underwent serial IVUS at baseline and after a 9-month follow-up. The authors studied 237 coronary segments containing untreated plaques that caused mild stenosis (<25% diameter narrowing) and were located at least 10 mm away from a previously stented lesion. Based on their IVUS appearance, lesions were qualitatively categorized as *soft*, *fibrous*, *calcified*, or *mixed*. Change in type of plaque (CTP) was defined as a difference in lesion category between the baseline and the follow-up IVUS examinations. In addition, the authors correlated CTP with major clinical events (cardiac death, myocardial infarction, and target vessel revascularization) during the subsequent 12 months. Overall, CTP was noted in 48 lesions (20.2%). The most common plaque type at baseline was *mixed* (39.2%), and CTP occurred more frequently in this subtype (52.1%). Mixed plaques evolved into any of the other phenotypes (*soft*, *fibrous*, or *calcified*), and conversely these other plaque types were transformed mostly into mixed plaques as well. There were no detectable differences in serial changes in luminal,

vessel, or plaque areas between lesions with or without CTP and, importantly, plaque subtype at baseline did not differ between groups. In multivariate analyses including conventional risk factors, type of coronary artery disease, medications received, baseline plaque characteristics, and various serum biomarkers, higher levels of glycated hemoglobin levels were associated with presence of CTP (odds ratio [OR]: 1.25, 95% confidence interval [CI] 1.01-1.56;  $P = .04$ ), whereas statin and glycoprotein IIb-IIIa inhibitors use was related to less frequent CTP (OR: 0.14, 95% CI 0.14-0.88,  $P = .02$  and OR 0.34, 95% CI 0.16-0.72,  $P = .004$ , respectively). During the 12-month clinical follow-up, major cardiovascular events developed in 13 (27.1%) patients with CTP versus 29 (15.3%) of those without ( $P < .001$ ). This was mainly due to higher incidence of revascularization (20.8% versus 13.8%,  $P = .008$ ) and a trend for fewer myocardial infarctions (6.3% versus 1.6%,  $P = .08$ ) in the CTP patients. No cardiac deaths occurred in either group. Finally, CTP was independently associated with cardiovascular events at 1 year after adjusting by age, diabetes type, and multivessel coronary disease (OR: 1.9, 95% CI 1.3-9.9;  $P = .01$ ).

The study by Jiménez-Quevedo et al.<sup>7</sup> provides important observations in diabetic atherothrombosis and raises interesting questions. First of all, notwithstanding the limitations and relatively gross characterization capabilities of grayscale IVUS, the fact that approximately 20% of coronary lesions changed qualitatively during a 9-month period highlights the dynamic nature of coronary atherosclerosis and is in agreement with recently published data. Using virtual histology IVUS at baseline and after a 12-month follow-up, a recent study examined 216 nonculprit lesions characterized by plaque burden > 40% in 99 patients (31% were diabetics). Coronary lesions evolved into a different type with a frequency ranging between 0 and 75% depending on baseline plaque type. Thin-cap fibroatheromata showed the most dynamic nature: of the 20 identified at baseline, 15 (75%) transformed into theoretically more stable phenotypes after 12 months. Conversely, 12 new thin-cap fibroatheromata developed from areas of prior intimal thickening or thick-cap fibroatheromata.<sup>8</sup>

Another interesting observation in the current study pertains to the fact that plaques evolved into not only more "unstable" subtypes (ie, soft plaques) but also frequently into theoretically more "stable" phenotypes (ie, calcified or fibrous lesions). One might expect that these opposite directional changes would be

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associated with more and fewer events on follow-up, respectively, and probably counteract one another in terms of clinical impact. However, and although the study was insufficiently powered to evaluate the effects of specific CTPs, it was the presence versus the absence of CTP that was independently related to cardiovascular events. Similarly, patients with “vulnerable” lesions such as soft plaques that did not experience CTP would be expected to still remain at higher risk of events. This did not seem to be the case since the authors specify (data not shown) that baseline plaque type distribution was comparable between patients with and without CTP. Nonetheless, outcomes were still lower in those whose lesion type did not evolve. Certainly, lack of change of nonculprit soft coronary plaques over similar periods of time has been previously reported in other studies.<sup>9</sup> These observations raise the thought-provoking hypothesis that CTP (either into more “stable” or “vulnerable” phenotypes) may be reflective of a more active and dynamic disease type, and perhaps deleterious in itself. Statins, glycoprotein IIb/IIIa inhibitors, and other therapies – through various lipid-lowering, anti-thrombotic, anti-inflammatory, etc. – mechanisms could help *passivate* the system, maybe not by necessarily transforming it into a less “vulnerable” one, but simply into a less dynamic one. This possibility would certainly deserve further testing in larger prospective studies, particularly to validate it with hard endpoints (death and myocardial infarction) as opposed to the less objective “need for revascularization.”

In the present study, impaired metabolic control as reflected by higher glycosylated hemoglobin concentrations was also associated with more frequent CTP. Although biologically plausible, this finding should be viewed in the context of recent clinical trials indicating that more intensive glucose lowering does not necessarily translate into improved cardiovascular prognosis, particularly for those with more advanced diabetes.<sup>10,11</sup> In addition, insulin dependent type 2 diabetes was associated with CTP in univariate analysis in this investigation, although statistical significance no longer persisted after adjustment for other covariates. Differential effects of different glucose lowering strategies have been described not only on IVUS-based plaque progression but also on clinical outcomes.<sup>12–15</sup> In addition, a prospective study of intermediate coronary lesions deemed “non-culprit” during an acute coronary syndrome was reported recently.<sup>16</sup> It identified IVUS-derived minimal lumen area under 4.0 mm<sup>2</sup>, percent plaque burden over 70%, and virtual histology algorithm-derived diagnosis of necrotic core as predictors of future coronary events, mainly repeat revascularization procedures for recurrent angina symptoms. It would have been great to have the specific report on the above IVUS-derived parameters from the current investigation.

In the future, other attractive investigations could center on the potential influence of specific oral agents (ie, glitazones, metformin, etc.) on dynamic changes in plaque type. Finally, it would be of interest to evaluate whether similar associations in CTP and outcomes can be replicated in the setting of nondiabetic atherothrombosis.

## CONFLICTS OF INTEREST

None declared.

## REFERENCES

- Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003;108:1664–72.
- Bosch X, Alfonso F, Bermejo J. Diabetes y enfermedad cardiovascular. Una mirada hacia la nueva epidemia del siglo XXI. *Rev Esp Cardiol*. 2002;55:525–7.
- Fuster V, Ibáñez B. Diabetes y enfermedad cardiovascular. *Rev Esp Cardiol*. 2008;8:35–44.
- Nicholls SJ, Tuzcu EM, Kalidindi S, Wolski K, Moon KW, Sipahi I, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. *J Am Coll Cardiol*. 2008;52:255–62.
- Philipp S, Bose D, Wijns W, Marso SP, Schwartz RS, König A, et al. Do systemic risk factors impact invasive findings from virtual histology? Insights from the international virtual histology registry. *Eur Heart J*. 2010;31:196–202.
- Hong YJ, Jeong MH, Choi YH, Ko JS, Lee MG, Kang WY, et al. Plaque characteristics in culprit lesions and inflammatory status in diabetic acute coronary syndrome patients. *JACC Cardiovasc Imaging*. 2009;2:339–49.
- Jiménez-Quevedo P, Suzuki N, Corros C, Ferrer MC, Angiolillo DJ, Alfonso F, et al. Evaluación de los cambios dinámicos de las placas coronarias y sus consecuencias clínicas en pacientes con diabetes mellitus tipo 2: un estudio de ecografía intravascular seriada. *Rev Esp Cardiol*. 2011;64:557–63.
- Kubo T, Maehara A, Mintz GS, Doi H, Tsujita K, Choi SY, et al. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. *J Am Coll Cardiol*. 2010;55:1590–7.
- Lee SY, Mintz GS, Kim SY, Hong YJ, Kim SW, Okabe T, et al. Attenuated plaque detected by intravascular ultrasound: clinical, angiographic, and morphologic features and post-percutaneous coronary intervention complications in patients with acute coronary syndromes. *JACC Cardiovasc Interv*. 2009;2:65–72.
- Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129–39.
- Zoungas S, Patel A, Chalmers J, De Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363:1410–8.
- Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA*. 2008;299:1561–73.
- Gerstein HC, Ratner RE, Cannon CP, Serruys PW, García-García HM, Van Es GA, et al., APPROACH Study Group. Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial. *Circulation*. 2010;121:1176–87.
- Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–15.
- Graham DJ, Ouellet-Hellstrom R, MacCurdy TE, Ali F, Sholley C, Worrall C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*. 2010;304:411–8.
- Stone GW, Maehara A, Lansky AJ, De Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–35.