

C-Reactive Protein and Restenosis of Drug-Eluting Stents. Intravascular Ultrasound Solves the Mystery

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In recent years, the connection between inflammation and arteriosclerosis has been the subject of frequent investigation. C-reactive protein (CRP) is by far the most widely studied inflammatory marker in practically every clinical context within the setting of cardiovascular disease. High CRP concentrations have been independently associated with a greater incidence of events, both in primary prevention and in patients with coronary artery disease, stable angina, or after acute coronary syndrome.¹⁻³

C-Reactive Protein and Restenosis

The inflammatory response caused by percutaneous coronary intervention in stent implantation has provided a suitable clinical model to assess the value of CRP concentrations to predict later events, and more specifically, restenosis. Nevertheless, the results from this field have not always been concordant, mainly due to the variety of methodologies used and the different sample sizes. The first published studies attempted to establish the value of baseline CRP to predict the incidence of mainly in-stent, clinical, or angiographic restenosis. Some studies found an association,⁴⁻⁶ whereas others did not.^{7,8} Later, other studies assessed the predictive value of CRP concentrations, but focused on the values obtained after revascularization procedures (at 24 h or even 1 month) or simply on the size of the increase, rather than baseline values.⁹⁻¹⁴ These studies showed that postprocedural CRP concentrations or the size of the increase have a more significant association with in-stent restenosis than baseline values.

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With the introduction of drug-eluting stents (DES), and given the antiinflammatory effect of the drugs released, studies were conducted to compare the inflammatory response induced by these stents (rapamycin- and paclitaxel-eluting stents) and conventional bare-metal stents. Our group published the first study of this kind,¹¹ and similar studies^{12,13,15,16} appeared shortly afterwards. The results of some of these studies have proven contradictory. Some found that the inflammatory response after DES implantation was of a magnitude comparable to that observed with bare-metal stents,¹¹⁻¹³ whereas other studies found that the response was lower.^{15,16} However, it is interesting that, in patients who had undergone rapamycin-eluting stent implantation, the baseline and the postintervention CRP values lost their predictive value for restenosis, unlike in bare-metal stents,^{11,12} although the power to predict death and infarction was maintained.¹⁶ Thus, it appears that DES also induce an inflammatory response similar to or lower than that induced by bare-metal stents, although the antiproliferative action of the drug attenuates their impact. A recently published study attempted to establish the origin of the increase in CRP concentrations after stent implantation. To this end, CRP concentrations were determined in samples extracted from the coronary sinus, demonstrating that the main source of the increase in plasma CRP values was the atheromatous plaque damaged by stent implantation and expansion.¹⁷

The clinical relevance of CRP concentrations to predict restenosis is greater with baseline values because they could become another factor to take into account—together with clinical (eg, diabetes) or anatomical factors (eg, lesion length)—when selecting the type of stent, whether this is a DES, involving greater or smaller late lumen loss, or a bare-metal stent. The cases of late thrombosis and its relationship to therapeutic noncompliance have made relevant some clinical selection criteria which were rarely taken into account before (eg, comorbidities, need for future non-cardiac surgery, etc), and, in this sense, CRP values could be a useful deciding factor in doubtful cases. Besides this, high CRP values have also been linked to a greater incidence of death and infarction in populations treated with DES.¹⁶

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All these studies used clinical events or angiographic restenosis as endpoints. Very few conducted an intravascular ultrasound (IVUS) study demonstrating a relationship between baseline CRP values and in-stent neointimal area or volume at follow-up. One exception is the study by Hong et al,¹⁸ which included 120 patients who had undergone bare-metal stent implantation. These authors found a significant relationship between high baseline CRP values and greater neointimal area at 6 months. The link between CRP values and restenosis was associated with the presence of soft plaque in the treated lesion (>80% of the plaque area had lower echogenicity than the adventitia and no calcium) which, in combination with a high CRP value, was the most powerful independent factor for restenosis. It should be emphasized that statin treatment was associated with less neointimal hyperplasia in the group with high CRP values, and not in the group with low values.

The diversity of results in these studies is strongly related to the objectives. The inability of some studies to detect a relationship between CRP values and restenosis may be due to unclear causal relationships and the use of clinical follow-up only. Although angiographic follow-up may increase the sensitivity of a given study, such sensitivity is not guaranteed even in large case-series (345-483 patients).^{7,8} On the other hand, quantifying neointimal hyperplasia by IVUS enables the detection of associations between CRP values and restenosis with a much smaller series of cases, as shown in the study cited.¹⁸

Following the same strategy, Lasave et al¹⁹ performed a study that included 40 patients which is published in this issue of *Revista Española de Cardiología*. They evaluated neointimal hyperplasia volume by 3-dimensional IVUS 4 months after zotarolimus-eluting stent implantation with the aim of determining if neointimal hyperplasia in the DES is associated with baseline CRP values,¹⁹ as already demonstrated with bare-metal stents.¹⁸ The authors found an association between CRP values and neointimal volume. The degree of correlation, excluding 1 case with an extreme value (outlier), was significant but modest ($r=0.4$). Nevertheless, this relationship was confirmed by the statistically significant result obtained by multivariate regression analysis and the significantly greater neointimal volume observed in the fourth quartile group when comparing baseline CRP values (15.8 μL) to the other 3 quartiles (4.8, 4.9, and 5.9 μL).

It is noteworthy that the use of IVUS was essential to obtaining positive results, given that the angiographic parameters were comparable between the different CRP quartiles, without any differences found in late loss (0.16, 0.18, 0.17, and 0.28 mm; $P=.15$) or in the rate of restenosis (0, 11, 0, and 11%; $P=.47$).

The choice of using the zotarolimus-eluting stent is a core issue in this DES study, because this type of stent inhibits neointimal hyperplasia significantly less than rapamycin- or paclitaxel-eluting stents. The use of the

latter, and especially rapamycin-eluting stents, would have very likely decreased the sensitivity of the study in detecting the relationship between CRP values and neointimal volume. This may also affect the generalizability of the results, and although there might be some class effects from bare-metal stents regarding their physiopathological effects in the arterial wall, DES can lead to specific physiopathological responses depending on the different drugs and polymers employed.

Analysis of the IVUS results showed that the patients in the higher CRP quartile—with subsequent greater neointimal hyperplasia—presented larger vessels and a tendency toward greater baseline plaque volume, and this difference was significant at follow-up. This finding is an outcome of the decrease in vessel volume and plaque volume in patients in the first and second quartiles, and a slight increase in plaque volume in those in the fourth quartile at follow-up. Nevertheless, the changes in these parameters between baseline and follow-up are not significant within each quartile, and thus the authors regard these differences as simply findings and not as a physiological mechanism that could explain the relationship between the highest CRP values and restenosis. The increase in vessel size and in-stent plaque observed with bare-metal stents was also assessed with DES, specifically polymer-controlled paclitaxel-eluting stents, demonstrating greater increases when moderate-release DES were used and similar increases when slow-release DES were used compared to bare-metal stents.²⁰

It is unfortunate that analysis of the IVUS results did not include the baseline and follow-up remodeling index values, since these, together with the cited data, could have shed light on the mechanism underlying the inflammation-CRP levels-restenosis relationship. It would also have been interesting to address the relationship between CRP values and neointimal hyperplasia at the stent edges.

The study was limited by its size, which was very small but sufficient to obtain positive results. The other studies which investigated the relationship between CRP values and restenosis needed hundreds of cases to find a relationship with clinical events or angiographic restenosis; a relationship which was not always found. This paper established such a relationship with only 40 cases, indicating the merits of IVUS in these types of study.

Another issue, recognized by the authors themselves, concerns follow-up at just 4 months, given that it is known that DES induce proliferative responses over a longer period. Clearly, if the study had been conducted at 9-12 months greater neointimal volume would have been demonstrated, the correlation with CRP values may have been higher, and may have demonstrated its potential association with possible changes in plaque volume and vessel volume.

Although the authors focus more on the research aspect of the study, namely, that this study can contribute to better understanding of the physiopathological processes underlying restenosis, of more practical clinical relevance, and a clearly bolder suggestion, would be to recommend incorporating baseline CRP values in the arsenal of information used by the interventionist when deciding the type of stent to use.

Finally, the study demonstrates that IVUS is very useful, in small-sized studies, to clarify issues that have remained open despite being the subject of large clinical trials. Thus, reference can be made, for example, to an association that was accepted for some time between the use of abciximab and a lower restenosis rate in diabetics—based on the results from major clinical trials—but which was finally rejected by a study which included 96 patients randomized to abciximab or placebo using IVUS volumetric analysis at 6 months.²¹

Intracoronary Ultrasound and Surrogate Endpoints

The study by Lasave et al¹⁹ did not use clinical or angiographic endpoints to demonstrate the relationship between CRP values and in-stent restenosis, but instead used neointimal hyperplasia volume assessed by IVUS, which is a surrogate endpoint.

Trials assessing the effectiveness of therapeutic cardiovascular interventions use clinical endpoints, but require more patients and time to demonstrate differences between current therapies and the new ones under study. Thus, before implementing a new treatment, drug, or device, and before conducting a long and expensive clinical trial, small trials are warranted to provide preliminary information on their effectiveness. These studies used endpoints associated with the incidence of clinical events, called surrogate endpoints, rather than clinical endpoints.

These are defined as the quantification of a physiopathological process that is characteristic of future clinical events. Surrogate endpoints make it possible to accurately predict the effect of therapy on a nonobserved final clinical endpoint. Thus, it is possible to detect statistically significant differences in studies that have much smaller samples and which are of shorter duration.²² A recently published article assessed the value of IVUS as a technique using surrogate endpoints to study new pharmacological interventions targeting arteriosclerosis.²³ Thus, a trial was conducted where IVUS demonstrated that one of the drugs under study was associated with reduced progression of coronary atherosclerosis.²⁴

When evaluating DES, the primary clinical endpoint regarding effectiveness is reducing the need for repeat revascularization procedures involving the treated segment. In-stent neointimal volume is a surrogate endpoint that fulfills the following characteristics:

- The surrogate endpoint should have a direct causal relationship with the clinical event (intimal hyperplasia → restenosis → new revascularization)
- It should be a variable whose magnitude bears a relation proportional to the incidence of the clinical event (greater neointimal volume → more restenosis → higher likelihood of revascularization)
- Surrogate endpoints can be evaluated through objective, accurate, and replicable techniques (IVUS fulfills these characteristics)

Nevertheless, regarding accuracy, the relationship between neointimal volume and repeat revascularization is not linear and, thus, as in angiographic late lumen loss, there are ranges of values where the statistically significant increases do not have an effect on the incidence of clinical events.

From the beginning, intracoronary ultrasound has been crucial in DES studies. The TAXUS I trial, which included 61 patients randomized to receive a paclitaxel-eluting stent or a bare-metal stent, did not find significant differences in angiographic restenosis²⁵ or in neointimal hyperplasia as assessed by IVUS. Something similar occurred in the FUTURE I study²⁶ which investigated the everolimus-eluting stent. In these trials, in-stent neointimal volume was 11% using the paclitaxel-eluting stent, and 1%-3% with the rapamycin-eluting stent²⁷; these differences between DES have not always been demonstrated in later comparative studies which only included clinical and angiographic endpoints.²⁸ Similarly, IVUS is essential in determining the impact of certain pharmacological interventions or specific biological markers in the context of in-stent restenosis.^{18,19,21}

Conclusion

The article by Lasave et al¹⁹ published in this issue of *Revista Española de Cardiología* provides a good example of the use of IVUS-based surrogate endpoints. With just 40 patients and conducted over a 4-month period, this work has provided results that support the etiological relationship between inflammation and in-stent restenosis. This improves our understanding of the processes involved in in-stent restenosis, which could prove useful when developing new models.

REFERENCES

1. Ridker P. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation*. 2001;103:1813-8.
2. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary

- syndromes: a TIMI 11^a substudy. Thrombosis in Myocardial Infarction. *J Am Coll Cardiol*. 1998;31:1460-5.
3. Bodi V, Sanchis J. La proteína C reactiva en el síndrome coronario agudo. Una mirada atrás para seguir avanzando. *Rev Esp Cardiol* 2006;59:418-20.
 4. Buffon A, Liuzzo G, Biasucci LM, Pasqualetti P, Ramazzotti V, Rebuzzi AG, et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. *J Am Coll Cardiol*. 1999;34:1512-21.
 5. Walter DH, Fichtlscherer S, Sellwig M, Auch-Schweik W, Schächinger V, Zeiher AM. Preprocedural C-reactive protein levels and cardiovascular events after coronary stent implantation. *J Am Coll Cardiol*. 2001;37:839-46.
 6. Chew DP, Bhatt DL, Robbins MA, Penn MS, Schneider JP, Lauer MS, et al. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous intervention. *Circulation*. 2001;104:992-7.
 7. Rittersma S, de Winter R, Koch K, Schotborgh C, Bax M, Hiede G, et al. Preprocedural C-reactive protein is not associated with angiographic restenosis or target lesion revascularization after coronary stent placement. *Clin Chem*. 2004;50:1589-96.
 8. Zairis M, Ambrose J, Manousakis S, Stefanidis A, Papadaki O, Biliyanou H, et al. For the GENERATION study group. The impact of plasma level of C-reactive protein, lipoprotein (a) and homocysteine on the long term prognosis after successful coronary stenting. *J Am Coll Cardiol*. 2002;40:1375-82.
 9. Gottsauner-Wolf M, Zasmata G, Hornykewycz S, Nikfardjam M, Stepan E, Wexberg P, et al. Plasma levels of C-reactive protein after coronary stent implantation. *Eur Heart J*. 2000;21:1152-8.
 10. Gaspardone A, Crea F, Versaci F, Tomai F, Pellegrino A, Chiariello L, et al. Predictive value of C-reactive protein after successful coronary artery stenting in patients with stable angina. *Am J Cardiol*. 1998;82:515-8.
 11. de la Torre Hernández JM, Sainz Laso F, Burgos V, Pérez T, Figueroa A, Zueco J, et al. Comparison of C-reactive protein levels after coronary stenting with bare metal versus sirolimus-eluting stents. *Am J Cardiol*. 2005;95:748-51.
 12. Dibra A, Ndrepepa G, Mehilli J, Dirschinger J, Pache J, Schunlen H, et al. Comparison of C-reactive protein levels before and after coronary stenting and restenosis among patients treated with sirolimus-eluting versus bare metal stents. *Am J Cardiol*. 2005;95:1238-40.
 13. Gaspardone A, Versaci F, Tomai F, Citone C, Proietti I, Gioffre G, et al. C-reactive protein, clinical outcome and restenosis rates after implantation of different drug-eluting stents. *Am J Cardiol*. 2006;97:1311-6.
 14. Hahn JY, Kim HS, Koo BK, Na SH, Chung JW, Youn TJ, et al. One month follow-up C-reactive protein may be a useful predictor of angiographic restenosis and long term clinical outcomes after bare metal stent implantation. *Int J Cardiol*. 2006;109:267-9.
 15. Gibson CM, Karmpaliotis D, Kosmidou I, Murphy SA, Kirtane AJ, Budiu D, et al. for the TIMI study group. Comparison of effects of bare metal versus drug-eluting stent implantation on biomarker levels following percutaneous coronary intervention for non-ST elevation acute coronary syndrome. *Am J Cardiol*. 2006;97:1473-7.
 16. Karha J, Bavry AA, Rajagopal V, Henderson MR, Ellis SG, Brenner SJ. Relation of C-reactive protein level and long term risk of death or myocardial infarction following percutaneous coronary intervention with a sirolimus eluting stent. *Am J Cardiol*. 2006;98:616-8.
 17. Ramadan MM, Kodama M, Mitsuma W, Ito M, Kashimura T, Ikrar T, et al. Impact of percutaneous coronary intervention on the levels of interleukin-6 and C-reactive protein in the coronary circulation of subjects with coronary artery disease. *Am J Cardiol*. 2006;98:915-7.
 18. Hong YJ, Jeong MH, Lim SY, Lee SR, Hong SN, Kim KH, et al. Relation of soft plaque and elevated preprocedural high-sensitivity C-reactive protein levels to incidence of in-stent restenosis after successful coronary artery stenting. *Am J Cardiol*. 2006;98:341-5.
 19. Lasave LI, Abizaid AC, Paiva e Maia J, de Ribamar-Costa J, Feres F, Mattos LA, et al. Asociación entre la concentración plasmática de proteína C-reactiva y el volumen de hiperplasia neointimal en pacientes tratados con implante de stent con liberación de zotarolimus. Análisis volumétrico con ultrasonido intracoronario tridimensional. *Rev Esp Cardiol*. 2007;60:923-31.
 20. Tanabe K, Serruys PW, Degertekin M, Guagliumi G, Grube E, Chan C, et al. Chronic arterial responses to polymer-controlled paclitaxel-eluting stents: comparison with bare metal stents by serial intravascular ultrasound analyses: data from the randomized TAXUS II trial. *Circulation* 2004;109:196-200.
 21. Chaves AJ, Sousa AG, Mattos LA, Abizaid A, Staico R, Feres F, et al. Volumetric analysis of in-stent intimal hyperplasia in diabetic patients treated with or without abciximab: results of the Diabetes Abciximab steNT Evaluation (DANTE) randomized trial. *Circulation*. 2004;109:861-6.
 22. Wittes J, Lakatos E, Probstfield J. Surrogate end points in clinical trials: cardiovascular diseases. *Stat Med*. 1989;8:415-25.
 23. Böse D, von Birgelen C, Erbel R. Intravascular ultrasound for the evaluation of therapies targeting coronary atherosclerosis. *J Am Coll Cardiol*. 2007;49:925-32.
 24. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071-80.
 25. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation*. 2003;107:38-42.
 26. Grube E, Sonoda S, Ikeno F, Honda Y, Kar S, Chan C, et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation*. 2004;109:2168-71.
 27. Mintz GS, Weissman NJ. Intravascular ultrasound in the drug-eluting stent era. *J Am Coll Cardiol*. 2006;48:421-9.
 28. Morice MC, Colombo A, Meier B, Serruys PW, Tamburino C, Guagliumi G, et al. Sirolimus-versus paclitaxel-eluting stents in de novo coronary artery lesions: The REALITY trial: a randomized controlled trial. *JAMA*. 2006;295:895-904.