ORIGINAL ARTICLE

C-reactive Protein Response and 5 Years of Follow-up after Elective Percutaneous Coronary Intervention Using Bare-metal, Drug-eluting, or Drug-eluting with Biodegradable Polymer Stents

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ABSTRACT

Introduction: There are numerous reports investigating the inflammatory response in vascular wall after stent implantation, although the results are still inconclusive when it comes to choosing the best type of stent, technique of stenting and also the time when C-reactive protein (CRP) reaches peak value and then returns to normal range. **Materials and Methods:** In this research, we compared inflammatory response after implantation of three types of stents: Bare-metal stents (BMS), drug-eluting stents (DES), and DESs with a biodegradable polymer (DES-B) in patients who underwent elective percutaneous coronary intervention (PCI). One hundred and twenty-four consecutive patients with stable coronary artery disease who underwent an elective PCI were included in this study. **Results:** Statistical analysis was possible in 32 patients with BMS, 55 with DES, and 19 with DES-B implanted. Concentration of CRP was measured before PCI, 24 and 72 h after the intervention; 5-year follow-up was carried out. It was recorded that 24 h after PCI, the level of CRP increased in 96% patients with BMS implanted ($P < 0.05$), 83% patients with DES ($P < 0.05$), and 58% with DES-B (ns). After 72 h the results were 90% ($P < 0.05$), 79% ($P < 0.05$), and 67% (ns) accordingly. The results also showed that implantation of BMS was associated with the greatest exacerbation of inflammatory response between 24 h and 72 h after PCI ($P < 0.01$). Moreover, implantation of DES-B was connected with the lowest impact on inflammation, especially when compared to BMS. Follow-up proved that DES-B was connected with a low risk of future revascularization, and DES was not superior to BMS in the long-term outcome. **Conclusion:** The choice of new generation DES-B in invasive cardiology is reasonable.

Key words: Biodegradable polymer, Coronary stents, C-reactive protein, Inflammatory response, In-stent restenosis, Percutaneous coronary intervention

INTRODUCTION

The severity of inflammation of the coronary artery wall after the percutaneous coronary intervention (PCI) seems to correlate with negative long-term outcomes. The research results demonstrate a clear relationship between PCI-related inflammatory response measured with C-reactive protein (CRP) and higher incidence of major adverse cardiovascular events such as myocardial infarction (MI) and also in-stent restenosis (ISR).[1,2] Gottsauner-Wolf *et al*. found that high circulating CRP levels that persisted >48 h increased the incidence of ISR within 6 months of the procedure.[2]

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Studies point out that CRP level reaches its peak value 24 h (Rebeiz *et al*.), 48 h (Kim *et al*., Gaspardone *et al*.), or 72 h (Munk *et al*.) after PCI and it takes up to 1 month after the procedure for CRP levels to return to normal range (Kang *et al*.).[3-7]

There is evidence linking the type of stent and the technique of stenting with the inflammatory response. Implantation of drug-eluting stent (DES) may be associated with significantly lower CRP levels than bare-metal stent (BMS);[3,4] however, in some studies, CRP levels did not differ significantly between the groups.[8] The statistically significant increase in plasma CRP, interleukin-6, and intercellular adhesion molecule-1 levels was the result of predilation before stenting.[9]

DES with biodegradable polymer (DES-B) is referred as 3rd generation DES, covered with a polymer as drug carrier that dissolves within months after implantation, facilitating endothelialization. In theory, DES-B should be connected with reduced inflammatory response, although there is no strong evidence at the moment.

The purpose of the study was to compare changes in circulating CRP levels 24 and 72 h after implantation of 3 types of stents: BMS, DES, or DES-B. Moreover, a 5-year follow-up was performed in terms of the need for re-revascularization.

MATERIALS AND METHODS

Patients

Between January and December 2014, 124 consecutive patients with stable coronary artery disease who underwent an elective PCI were included in this study. The local ethical committee approved the protocol and patients gave written informed consent. Patients' blood plasma CRP levels were assessed before PCI, 24 h and 72 h after PCI. The choice of the stent depended on the decision of the physician performing PCI.

Types of stents used in the study

Participants were divided into 3 cohort groups depending on which type of stent was used.

Bare-metal stent (BMS)

First generation associated with high risk of ISR. Some research points to the prevalence of 20–30%.[10] However, after BMS implantation, patients have shorter exposure to dual antiplatelet therapy and thus have lower bleeding risk.[10] Moreover, the costs of BMS are markedly lower than other types of stents. Nowadays, BMS is very rarely used.

Drug-eluting stent (DES)

This type of stent is associated with reduced inflammatory response in vascular wall because of antiproliferative drug coating (e.g.everolimus).[11] Therefore, there is a reduced risk of ISR.[12] On the other hand, DES implantation is associated with impairment of endothelial regeneration, which extends the time of the wound-healing process in injured vessels.[13] This phenomenon leads to late-phase inflammation, meaning antiproliferative drugs on the DES disappear, and wound has not healed yet.[14]

Drug-eluting stents with biodegradable polymer (DES-B)

This is a modified DES, that has a bioabsorbable polymer instead of permanent. The polymer, after fulfilling its function (controlled drug release), is degraded, which reduces endothelial irritation. This alteration should reduce the inflammatory response in the coronary vascular wall. On that account, vascular wall injury is of shorter duration.[15]

Follow-up

Five-year follow-up was conducted in terms of the need for re-revascularization. It was made on the basis of a hospital electronic database.

Statistical analysis

Post hoc statistical tests were performed by analysis of variance and also Spearman's rank correlation coefficient was used.

RESULTS

Patients were divided into 3 cohort groups, depending which type of stent was used. Five patients with more than one stent implanted and 13 patients with plain balloon angioplasty were excluded from the analysis. Thirty-two patients had BMS implanted, 55 DES, and 19 DES-B. Data on CRP levels were available in 26 (20) patients with BMS, 46 (33) with DES, and 12 (15) with DES-B, 24 h (72 h) after PCI. Demographic data of the patients included in statistical analysis are presented in Table 1. The alterations in blood plasma levels of CRP and the direction of changes are shown in Table 2. Detailed comparison between CRP concentrations after implantation of different types of stents is shown in Figure 1. There is a positive correlation [Figure 2] between duration of PCI and CRP concentration 72 h after that procedure (r=0,623, $P < 0.05$). If predilation and/or postdilation were used, CRP level raised significantly 24 h and 72 h after PCI [Figure 3]. Five-year clinical follow-up is presented in Table 3.

DISCUSSION

Stent implantation is associated with injury of the endothelium and inflammatory response in the vascular wall. This in turn is connected with atherosclerotic process and ISR and as a consequence with a higher risk of MI.[16] These

Table 1: Demographic table, abbreviations

Characteristics	DES group (*n*=55)	DES-B group (*n*=19)	BMS group (*n*=32)	*P*-value
Age (years)	63.2±10.2	61.9±9.4	64.8±9.3	ns
Male gender (%)	13 (24)	5 (26)	13 (41)	ns
BMI (kg/m^2)	30.2±4.8	28.2±4.4	29.4±4.4	ns
Current smoker (%)	11 (20)	3 (16)	6 (19)	ns
Diabetes (%)	20 (36)	4 (21)	10 (31)	ns
Hypertension (%)	42 (76)	13 (68)	23 (72)	ns
LVEF (%)	51.1±9.4	54.9±6.4	54.3± 6.7	ns
Prior MI (%)	37 (67)	11 (58)	14 (44)	ns
eGFR (ml/min/1,73 m^2)	108.4±37.5	113±40.8	103.8±33.9	ns
Multi-vessel CAD (%)	29 (53)	9 (47)	18 (56)	ns
Statin therapy (%)	51 (93)	16 (84)	27 (84)	ns
HGB (g/dl)	14.1±1.1	14.04±1.4	14±1.5	ns

BMI: Body mass index, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, eGFR: Estimated glomerular filtration rate, CAD: Coronary artery disease, HGB: Hemoglobin

Table 2: Directions of change in CRP levels 24 h and 72 h after percutaneous coronary intervention

dCRP-24	Increase (%)	Decrease (%)	*P*-value
BMS	1 (4)	25 (96)	0,001
DES-B	5 (42)	7 (58)	ns
DES	8 (17)	38 (83)	0,001
dCRP-72	**Increase (%)**	**Decrease (%)**	***P*-value**
BMS	2 (10)	18 (90)	0,01
DES-B	5 (33)	10 (67)	ns
DES	7 (21)	26 (79)	0.01

Table 3: Major cardiovascular events recorded during 5-year clinical follow-up

Events within 5-year follow-up	DES group (*n*=55)	DES-B group (*n*=19)	BMS group (*n*=32)
Need of revascularization (percutaneous coronary intervention or CABG) (%)	13 (24)	3 (15)	6 (19)

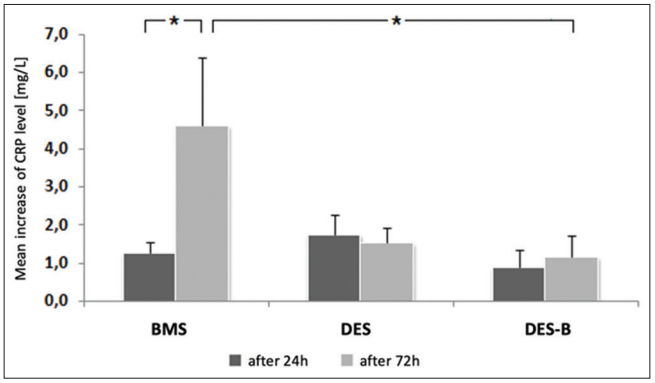

Figure 1: Mean increase of C-reactive protein concentration depending on stent type, 24 h after percutaneous coronary intervention (PCI) and 72h after PCI

clinical complications are especially related to the prolonged time of inflammation, namely long-lasting elevated CRP concentration.[2] In our study, BMS implantation was associated with considerable inflammatory response, which was significantly more extensive after 72 h than after 24 h. This finding is accordant with other clinical studies.[4] After DES implantation, inflammatory response was not so evident and with similar severity between 24 h and 72 h. The most interesting finding of this study is that after DES-B implantation, CRP increase was the smallest and was statistically significant when compared to BMS; however, it did not differ significantly from that observed in DES group.

In our study, the positive relationship between inflammatory response and predilation and/or postdilation during PCI was observed, which is consistent with another research.[9] Furthermore, duration of PCI procedure turned out to have a significant impact on plasma CRP levels.

In our study, 5-year follow-up showed that patients with DES-B were at the lowest risk of future revascularization. As far as we know, there is a lack of studies which assessed the need of re-revascularization in 5-year follow-up. NORSTENT trial has found that there were no significant differences in the outcome of death from any cause or nonfatal spontaneous MI between BMS group and DES group for 6 years follow-up.[17] The results of randomized, large clinical trial (BIOSTEMI) confirmed safety and efficacy of DES-B in comparison to DES.[18]

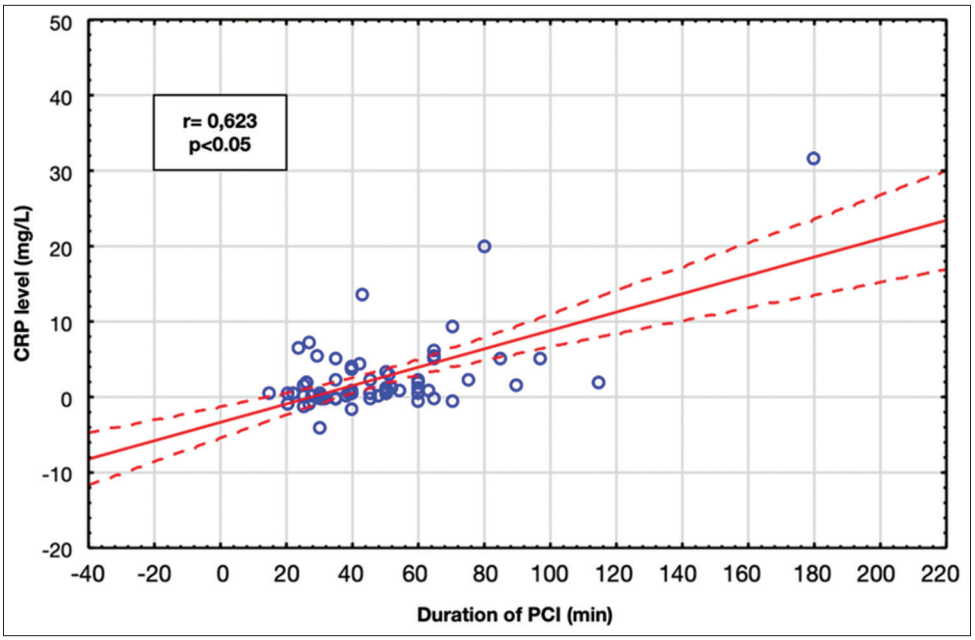

Figure 2: Correlation between duration of percutaneous coronary intervention and C-reactive protein concentration

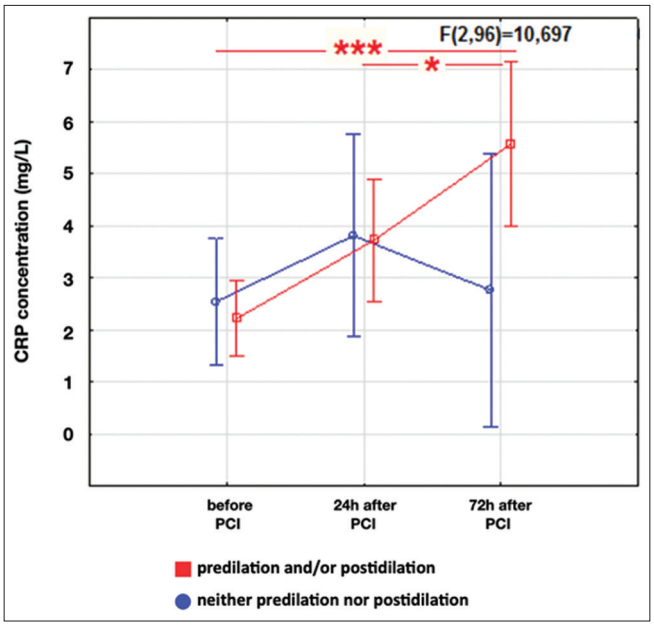

Figure 3: C-reactive protein concentration-dependent on predilation and/or postdilation

Our results seem to confirm that long procedures with large vessel damage and the use of BMS are associated with a higher risk of complications in the future. Moreover, the choice of new generation DES-B in invasive cardiology is reasonable.

Limitation of the study

The main limitation of this study is a small number of patients included in the study.

CONCLUSION

We conclude that the choice of DESs with biodegradable polymer for elective PCI may be correlated with weak immune response and low risk of the future need of revascularization. We provided baseline data for further larger, prospective, and randomized studies and also bring back attention to biodegradable polymers used in invasive cardiology.

Declarations

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional ethical committee. Written informed consent was obtained from all patients before their inclusion in the study.

REFERENCES

1. Oemrawsingh RM, Cheng JM, Akkerhuis KM, Kardys I, Degertekin M, van Geuns RJ, *et al*. High-sensitivity C-reactive protein predicts 10-year cardiovascular outcome after percutaneous coronary intervention. Eur Intervent 2016;12:345-51.
2. Gottsauner-Wolf M, Zasmeta 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.
3. Rebeiz AG, Zoghbi E, Harb R, Youhanna S, Skouri HN, Dimassi A, *et al*. Comparison of the systemic levels of inflammatory markers after percutaneous coronary intervention with bare metal versus sirolimus-eluting stents. J Interv Cardiol 2009;22:169-74.

4. Kim JY, Ko YG, Shim CY, Park S, Hwang KC, Choi D, *et al*. Comparison of effects of drug-eluting stents versus bare metal stents on plasma C-reactive protein levels. Am J Cardiol 2005;96:1384-8.
5. 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.
6. Munk PS, Breland UM, Aukrust P, Skadberg O, Ueland T, Larsen AI. Inflammatory response to percutaneous coronary intervention in stable coronary artery disease. J Thromb Thrombolysis 2011;31:92-8.
7. Kang WC, Ahn TH, Moon CI, Han SH, Shin EK, Kim JS, *et al*. Comparison of inflammatory markers and angiographic outcomes after implantation of sirolimus and paclitaxel-eluting stents. Heart 2009;95:970-5.
8. de la Torre-Hernandez JM, Sainz-Laso F, Burgos V, Perez 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.
9. Sakr SA, Ramadan MM, El-Gamal A. The inflammatory response to percutaneous coronary intervention is related to the technique of stenting and not the type of stent. Egypt Heart J 2016;68:37-43.
10. Brancati MF, Burzotta F, Trani C, Leonzi O, Cuccia C, Crea F. Coronary stents and vascular response to implantation: Literature review. Pragmat Obs Res 2017;8:137-48.
11. Klawitter J, Nashan B, Christians U. Everolimus and sirolimus in transplantation-related but different. Expert Opin Drug Saf 2015;14:1055-70.
12. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, *et al*. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: A quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2001;103:192-5.
13. Finn AV, Nakazawa G, Joner M. Vascular responses to drug eluting stents: Importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500-10.
14. Taguchi I, Yoneda S, Abe S, Toyoda S, Nasuno T, Nishino S, *et al*. The late-phase inflammatory response after drug-eluting stent implantation. Heart Vessels 2014;29:213-9.
15. Kalra A, Rehman H, Khera S, Thyagarajan B, Bhatt DL, Kleiman NS, *et al*. New-generation coronary stents: Current data and future directions. Curr Atheroscler Rep 2017;19:14.
16. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple risk factor intervention trial. Am J Epidemiol 1996;144:537-47.
17. Saleh N, Svane B, Jensen J, Hansson LO, Nordin M, Tornvall P. Stent implantation, but not pathogen burden, is associated with plasma C-reactive protein and interleukin-6 levels after percutaneous coronary intervention in patients with stable angina pectoris. Am Heart J 2005;149:876-82.
18. Wiseth R, Bønaa KH. Potential implications of NORSTENT (Norwegian coronary stent trial) in contemporary practice. Circulation 2017;136:701-3.
19. Iglesias JF, Muller O, Heg D, Roffi M, Kurz DJ, Moarof I, *et al*. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): A single-blind, prospective, randomised superiority trial. Lancet 2019;394:1243-53.

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