European Heart Journal (2016) **37**, 2713–2721
doi:10.1093/eurheartj/ehw256

Beneficial effects of long-acting nifedipine on coronary vasomotion abnormalities after drug-eluting stent implantation: The NOVEL study

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Received 22 April 2015; revised 26 April 2016; accepted 31 May 2016; online publish-ahead-of-print 28 June 2016

Aims It is widely known that drug-eluting stents (DES) induce coronary vasomotion abnormalities. We have previously demonstrated that chronic treatment with long-acting nifedipine suppresses coronary hyperconstricting responses induced by the first-generation DES (e.g. sirolimus- and pacritaxel-eluting stents) through inhibition of vascular inflammation in pigs. To examine whether this is also the case with the second-generation DES (everolimus-eluting stents, EES) in humans, the most widely used DES in the world, we conducted a prospective, randomized, multicentre trial, termed as the NOVEL Study.

Methods and results We evaluated 100 patients with stable angina pectoris who underwent scheduled implantation of EES in the left coronary arteries. They were randomly assigned to receive either conventional treatments alone or additionally long-acting nifedipine (10–60 mg/day) ($n = 50$ each). After 8–10 months, 37 patients in the control and 38 in the nifedipine group were examined for coronary vasoreactivity to intracoronary acetylcholine (ACh) by quantitative coronary angiography after 48-h withdrawal of nifedipine. Coronary vasoconstricting responses to ACh were significantly enhanced at the distal edge of EES compared with non-stented vessel ($P = 0.0001$) and were significantly suppressed in the nifedipine group compared with the control group ($P = 0.0044$). Furthermore, the inflammatory profiles were also improved only in the nifedipine group, which evaluated by serum levels of high-sensitivity CRP ($P = 0.0001$) and adiponectin ($P = 0.0039$).

Conclusions These results indicate that DES-induced coronary vasomotion abnormalities still remain an important clinical issue even with the second-generation DES, for which long-acting nifedipine exerts beneficial effects associated with its anti-inflammatory effects. Trial Registration: This study is registered at the UMIN Clinical Trial Registry (UMIN-CTR; ID=UMIN000015147).

Keywords Drug-eluting stents • Coronary spasm • Calcium channel blockers

Introduction

Drug-eluting stents (DES) have been widely used over the past decades with the marked reduction of in-stent restenosis (ISR) and need of revascularization after percutaneous coronary intervention (PCI).[1] However, the use of the first-generation sirolimus- and paclitaxel-eluting stents (SES/PES) raised several concerns about the safety issue, including late stent thrombosis (LST)[2] and impairment of coronary vasomotion.[3–7] Indeed, enhanced coronary vasoconstriction in response to intracoronary acetylcholine (ACh)[4] or

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exercise stress[3] have been noted in the coronary segments adjacent to DES but not in those to bare-metal stents.[3,4] It has also been reported that severe coronary spasm at the stented vessel could cause serious adverse cardiac events in the chronic phase following DES implantation.[7] We have previously demonstrated that activation of Rho-kinase, a downstream effector of the small GTP-binding protein Rho, plays a central role in the molecular mechanism of coronary spasm[8] and DES-induced coronary hyperconstricting responses as well.[5,6] Recently, it has been shown that the second-generation DES succeeded in ameliorating the adverse effect of the first-generation SES or PES with resultant better clinical performance.[9] However, it remains to be elucidated whether the second-generation DES have actually resolved the problem of the first-generation SES/PES,[10] and if not, what medication is effective to ameliorate the DES-induced coronary vasomotion abnormalities.

Long-acting calcium channel blockers (CCBs) are widely used as the first-line agents for vasospastic angina (VSA).[11] Previous studies (e.g. ACTION and ENCORE trials) demonstrated that long-acting nifedipine exerted cardiovascular protective effects through inhibition of vascular inflammation and improvement of endothelial function.[12,13] Furthermore, we have recently reported that long-acting nifedipine suppresses PES-induced coronary hyperconstricting responses in pigs *in vivo* associated with improvement of PES-induced inflammatory changes and Rho-kinase activation.[14]

In the present study, we thus aimed to examine whether long-acting nifedipine exerts the vasculoprotective effects on the coronary arteries implanted with the second-generation DES in patients with coronary artery disease (CAD) and also improves their long-term prognosis in a prospective, randomized, multicentre trial, termed as the NOVEL Study.

Methods

The Nifedipine on Coronary Vascular Function after Drug-Eluting Stent Implantation (NOVEL) Study was a prospective, randomized, multicentre study and was conducted following the ethical principles in the Declaration of Helsinki (UMIN000015147). The study protocol was approved by each institutional ethics committee of the nine participating hospitals in Japan (Supplementary material online, p. 16–17).

Study design

We enrolled patients with stable angina pectoris aged ≥20 years who underwent scheduled implantation of everolimus-eluting stents (EES) in the left coronary arteries (LCA). The following patients were excluded: (i) acute coronary syndrome, (ii) VSA, (iii) heart failure with reduced ejection fraction (EF < 40%), (iv) severe liver and/or renal dysfunction, (v) intolerance to CCBs, and (vi) previous stent implantation in the target vessel. All patients were randomly assigned to either the control group treated with conventional therapies alone (aspirin, clopidogrel, renin–angiotensin system inhibitors (RASI), and statins) or the nifedipine group treated with additional long-acting nifedipine to the conventional therapies, with a 1:1 ratio through stratification by sex, age, baseline systolic blood pressure, and diabetes mellitus in each participating hospital. Primary endpoint was coronary vasoconstricting response to ACh in the coronary segments adjacent to EES. Secondary endpoints were defined as composite of major adverse cardiac events, including cardiac death, non-fatal myocardial infarction (MI), and target lesion or vessel revascularizations (TLR/TVR).

Coronary vasomotor responses to intracoronary acetylcholine

At 8–10 months after EES implantation, coronary vasomotor responses to ACh were examined as previously reported in detail.[6] Long-acting nifedipine was discontinued at least 48 h before the study. Quantitative coronary angiography (QCA) was performed by two independent observers who were blinded to the assignment of patients. Coronary segments assessed by QCA included the stented segment (within 20 mm apart from proximal and distal stent edges) and a non-stented segment of LCA as a reference site.[14] Coronary vasomotor responses to ACh were quantified as per cent change in luminal diameter compared with that after intracoronary isosorbide dinitrate (ISDN).

Inflammatory and anti-inflammatory biomarkers

To clarify the effects of long-acting nifedipine on systemic inflammatory status, we measured serum levels of high-sensitivity C-reactive protein (hsCRP) and plasma levels of pentraxin-3 (PTX3) as inflammatory markers,[15] and adiponectin as an anti-inflammatory marker[16] at three times, including baseline, 3 and 8–10 months after PCI.

Statistical analysis

Based on the results of the previous studies,[6,12–14] we expected that adding long-acting nifedipine would achieve 10% reduction in coronary vasoconstricting responses to ACh compared with conventional therapies alone. The assumptions used for power calculations required a sample size of 37 patients per treatment group to provide 80% power (assuming an SD of 15.0%) to detect 10% difference in coronary vasoconstricting responses with a 5% type I error rate for a two-sided test. With an anticipated dropout rate of ∼25%, enrolment of 50 patients per treatment group (100 randomized patients in total) was specified to provide an adequate number of patients for evaluable ACh provocation test. Continuous variables are expressed as mean ± SD and categorical variables as percentages. Unpaired Student's *t*-test for normal distribution and Wilcoxon tests for asymmetric distribution were used to analyse differences in continuous variables. χ^2 test or Fisher's exact test was used for categorical variables. Comparisons of inflammatory and anti-inflammatory markers at three time points were performed with repeated measures analysis of variance following multiple comparisons by Turkey Honestly significant difference test. A *P*-value of <0.05 was considered to be statistically significant (refer to Supplementary material for further information).

Results

Patient flow and characteristics

Between November 2011 and September 2013, a total of 146 patients who were eligible for the inclusion criteria and gave written informed consent were enrolled. In the present study, however, in accordance with the ethical committee recommendation, we turned the initially enrolled and randomized 100 patients into the objects of comparative evaluation. Flow chart of this study is shown in *Figure 1*. In both the control and the nifedipine groups, 50 patients were finally assigned. During the time between patient randomization and follow-up CAG, 12 patients in the control group and 11 in the nifedipine group dropped out because of adverse events, violation of the protocol for stent implantation or withdrawal of consent. Thus, follow-up CAG was performed in 38 patients in the control group and 39 in the nifedipine group; however, one patients in the

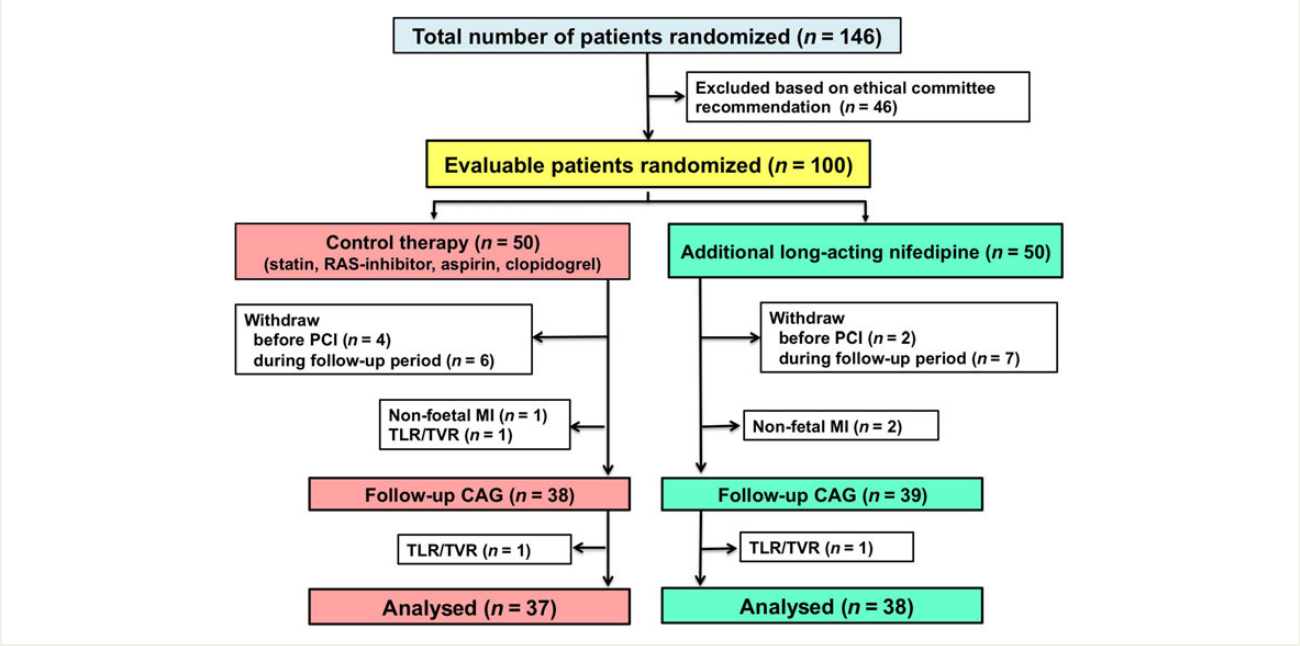

Figure 1 Patient flow diagram. RAS, renin–angiotensin system; PCI, percutaneous coronary intervention; CAG, coronary angiogram; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

each group needed TLR/TVR. Finally, coronary vasomotor responses to ACh were examined in 37 patients in the control and 38 in the nifedipine group (*Figure 1*). Patient characteristics and medications at baseline are summarized in *Table 1*. All data were comparable between the two groups. Moreover, we found no difference in mean blood pressure or heart rate at the follow-up study between the two groups (*Table 1*).

Angiographic and procedural profiles

Angiographic and procedural characteristics are shown in *Table 2*. The nifedipine group tended to be implanted the EES in LAD more frequently compared with the control group, although statistically not significant. Although the stenotic severity of target lesion was slightly serious in the control group compared with the nifedipine group, the other lesion and procedural characteristics were all comparable between the two groups.

Coronary vasomotor responses to intracoronary acetylcholine

Intracoronary ACh caused severe coronary spasm requiring immediate intracoronary ISDN administration more frequently in the control group ($n = 19$, 51.4%) compared with the nifedipine group ($n = 9$, 23.7%) ($P = 0.0175$) (*Figure 2*). Thus, not all patients received all three doses of ACh, seven in the control group (21.2%), and five in the nifedipine group (14.3%) received the initial and lowest dose of ACh (25μg) alone, while seven (23.3%) and four (12.1%) in the control and the nifedipine groups received the intermediate dose of ACh (50μg), respectively. Importantly, ACh-induced vasoconstriction at the segment distal to the EES was suppressed in the nifedipine group compared with the control group (*Figure 2*). Quantitative coronary angiography measurements for coronary vasomotor responses to ACh are summarized in *Table 3* and *Figures 3*. Serial changes in the absolute value of minimum lumen diameter in the region of interest are also shown in Supplementary material online, *Table S1* and *Figure S1*. The results are comparable with those with using %change in diameter at the selected point. Quantitative coronary angiography analysis showed that coronary vasoconstricting responses to ACh were significantly enhanced at the distal edge to the EES compared with the non-stented vessel in both groups. In subgroup analysis for LAD and LCX, although the constricting effect of ACh was more pronounced in the LAD, the per cent reduction of constriction following nifedipine treatment was comparable between the two arteries (LAD, $14.7 \pm 4.8\%$ vs. LCX, $15.8 \pm 7.1\%$, $P = 0.82$) (Supplementary material online, *Figure S2*). Furthermore, increasing number of EES tended to correlate with greater vasoconstriction at the distal edge to EES in the control group, whereas no such tendency was noted in the nifedipine group (Supplementary material online, *Figure S3*). In contrast, no significant difference in response to ACh was noted between the proximal segments of EES and the non-stented vessel. Maximum coronary vasodilation to ISDN from baseline was comparable between the two groups (*Table 3*).

Inflammatory and anti-inflammatory biomarkers

Serial changes in serum levels of inflammatory and anti-inflammatory biomarkers are shown in *Figure 4* and Supplementary material online, *Figure S4*. At baseline, there was no difference in the levels of adiponectin, hsCRP or PTX3 between the control and the nifedipine groups. When compared with baseline, the treatment

Table 1 Baseline characteristics

	Control (n = 37)	Nifedipine (n = 38)	P-value
Age	69.7 ± 10.2	67.6 ± 9.2	0.37
Male (%)	23 (62.2)	25 (65.8)	0.81
Hypertension, n (%)	28 (75.7)	33 (86.8)	0.25
Mean blood pressure (mmHg)			
At baseline	97.2 ± 15.2	95.2 ± 13.8	0.55
At follow-up study	94.3 ± 13.3	91.0 ± 13.8	0.16
Heart rate (beat per minutes)			
At baseline	74.3 ± 12.8	73.1 ± 12.5	0.79
At follow-up study	70.9 ± 11.5	70.1 ± 12.1	0.54
Dyslipidaemia, n (%)	21 (56.8)	19 (50.0)	0.65
Diabetes merits, n (%)	18 (48.7)	19 (50.0)	1.0
Smoking, n (%)	7 (18.9)	11 (29.0)	0.42
Previous myocardial infarction, n (%)	12 (33.3)	10 (26.3)	0.61
Laboratory findings			
Triglyceride (mg/dL)	135.8 ± 58.0	145.5 ± 72.1	0.84
LDL-cholesterol (mg/dL)	86.4 ± 24.3	82.0 ± 30.0	0.49
HDL-cholesterol (mg/dL)	49.8 ± 13.0	51.0 ± 20.4	0.56
Total cholesterol (mg/dL)	161.9 ± 25.5	159.6 ± 32.1	0.67
White blood cell ($\times 10^3/\mu L$)	6178 ± 1910	5876 ± 1360	0.63
Creatinine (mg/dL)	0.81 ± 0.18	0.81 ± 0.20	0.78
Baseline medications			
Statins, n (%)	35 (94.6)	38 (100.0)	0.24
RAS inhibitors, n (%)	33 (89.2)	35 (92.1)	0.72
β-blockers, n (%)	19 (51.4)	12 (31.6)	0.10
Nitrates, n (%)	13 (35.1)	15 (39.5)	0.86

Results are expressed as mean ± SD.
RAS, renin–angiotensin system; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2 Procedural and angiographic findings

	Control (n = 37)	Nifedipine (n = 38)	P-value
Target lesion			
LAD	26 (70.3%)	33 (86.8%)	0.09
LCX	11 (29.7%)	5 (13.1%)	
Type B2/C lesion, n (%)	28 (75.7%)	27 (71.1%)	0.80
Number of stents/lesion	1.4 ± 0.6	1.2 ± 0.5	0.38
Stent size (mm)	2.9 ± 0.3	3.0 ± 0.4	0.23
Stent length (mm)	26.7 ± 11.7	27.4 ± 13.0	0.87
Reference vessel diameter (mm)	2.50 ± 0.40	2.59 ± 0.40	0.39
Lesion MLD (mm)	0.92 ± 0.33	1.09 ± 0.33	0.03
% diamter stenosis (%)	63.5 ± 11.7	57.9 ± 11.1	0.04
Lesion length (mm)	22.0 ± 12.4	19.5 ± 10.6	0.36
Acute gain (mm)	1.46 ± 0.39	1.30 ± 0.39	0.65
Late loss (mm)	0.20 ± 0.32	0.11 ± 0.33	0.79

Results are expressed as mean ± SD.
LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MLD, minimum lumen diameter.
Stent diameter was calculated by averaging the diameters at the proximal edge, mid portion, and distal edge of the stented coronary artery.

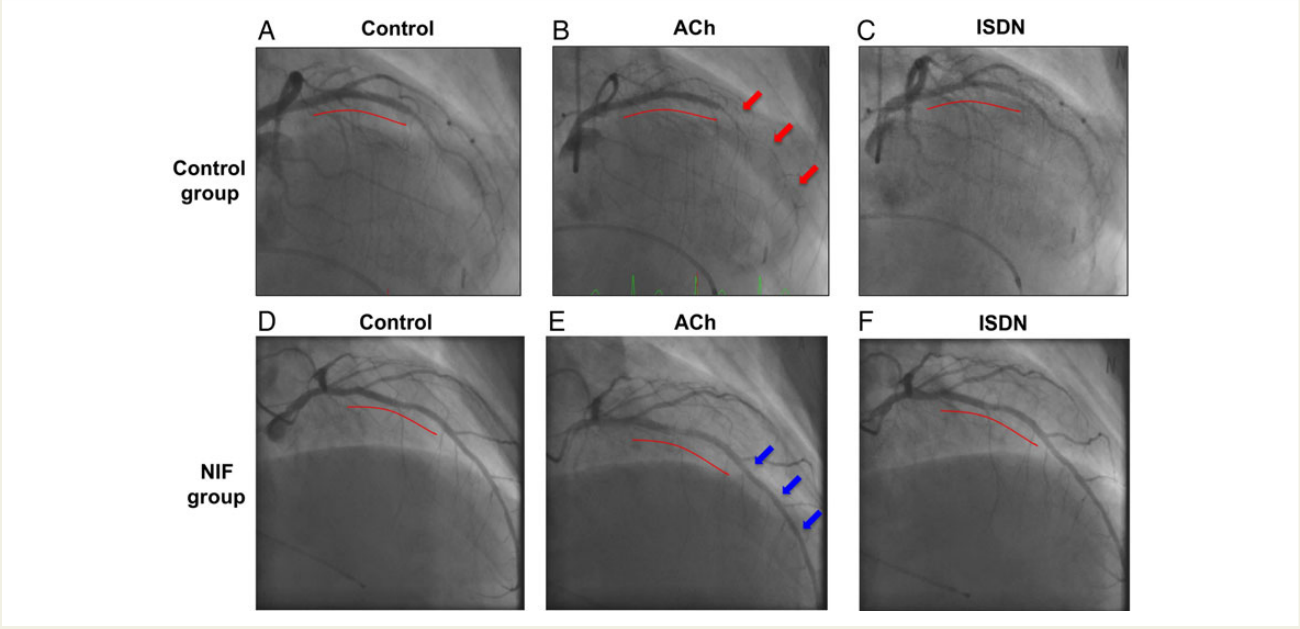

Figure 2 Nifedipine attenuates everolimus-eluting stent-induced coronary hyperconstricting responses. Representative left coronary angiograms of a patient in the control group (*A*–*C*) and a patient of the nifedipine group (*D*–*F*), under control condition (*A*, *D*), after intracoronary acetylcholine (*B*, *E*) and isosorbide dinitrate (*C*, *F*). Red lines indicate the site of everolimus-eluting stent implantation. The angiogram after acetylcholine infusion in the control group (*B*) showed severe vasoconstriction along the distal segment adjacent to the stent (red arrows), whereas no severe vasoconstriction was noted in the nifedipine group (blue arrows) (*E*).

Table 3 % Changes in diameter response to acetylcholine

	Control	Nifedipine	*P*-value
ACh 25 μg i.c.	$n = 33$	$n = 33$	
Proximal edge (%)	-22.7 ± 20.8	-17.8 ± 16.3	0.38
Distal edge (%)	-42.2 ± 19.1*	-28.1 ± 17.9**	0.0044
Non-stented vessel (%)	-20.5 ± 16.7	-15.0 ± 16.0	0.29
ACh 50 μg i.c.	$n = 30$	$n = 33$	
Proximal edge (%)	-19.4 ± 17.1	-16.5 ± 15.8	0.43
Distal edge (%)	-43.9 ± 23.5*	$-27.6 \pm 15.7^{\dagger}$	0.0030
Non-stented vessel (%)	-17.2 ± 15.0	-16.3 ± 16.8	0.90
ACh 100 μg i.c.	$n = 23$	$n = 29$	
Proximal edge (%)	-23.8 ± 19.1	-18.7 ± 14.3	0.21
Distal edge (%)	-43.9 ± 19.3*	-32.6 ± 16.7**	0.060
Non-stented vessel (%)	-17.9 ± 15.8	-20.9 ± 12.7	0.31
ISDN	$n = 37$	$n = 38$	
Proximal edge (%)	22.8 ± 25.2	24.0 ± 22.9	0.47
Distal edge (%)	34.1 ± 34.2	27.6 ± 27.9	0.40
Non-stented vessel (%)	12.8 ± 15.1	14.6 ± 17.4	0.55

Results are expressed as mean ± SD.
%Change in diameter = {Lumen diameter (ACh) − lumen diameter (ISDN)}/lumen diameter (ISDN) × 100.
*$P < 0.0005$ vs. non-stented vessel; ** $P < 0.01$; $^{\dagger}P < 0.05$.
ACh, acetylcholine; ISDN, isosorbide dinitrate.

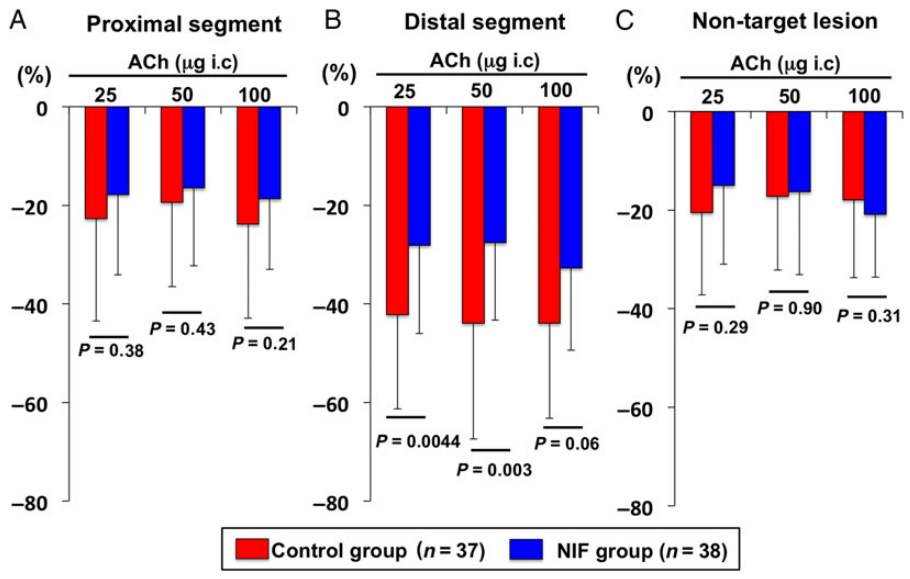

Figure 3 Coronary vasomotor response to intracoronary acetylcholine. Coronary vasoconstriction to intracoronary acetylcholine at the proximal (*A*) and the distal edges (*B*) adjacent to everolimus-eluting stent and at the non-stented vessel as a reference (*C*). The extent of coronary vasoconstriction is expressed as % changes in diameter from the level with intracoronary isosorbide dinitrate. Results are expressed as mean ± SD. *P*-values are for unpaired Student's *t*-test for normal distribution and Wilcoxon tests for asymmetric distribution.

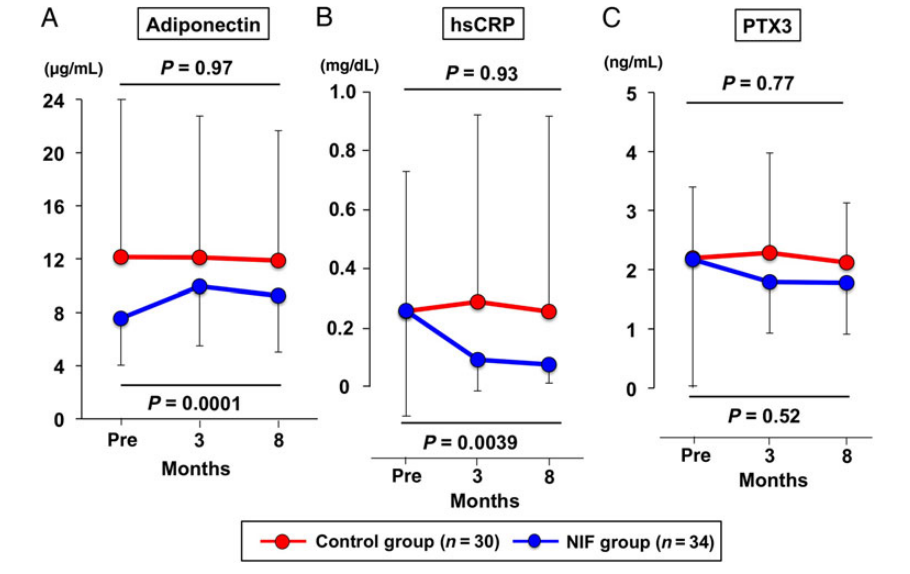

Figure 4 Impact of long-acting nifedipine on inflammatory profiles. Time-course analysis for an anti-inflammatory marker, adiponectin (*A*), and inflammatory markers, high-sensitivity CRP (hsCRP) (*B*) and pentraxin-3 (PTX3) (*C*). Results are expressed as mean ± SD. *P*-values are for repeated measure analysis of variance.

with long-acting nifedipine significantly increased adiponectin level ($P = 0.0001$) and decreased hsCRP level ($P = 0.0039$) during the follow-up period, whereas no such change was noted in the control group.

Secondary endpoints

During the study period, three patients in the control group (6.0%) and three in the nifedipine group (6.0%) had the secondary endpoints (Supplementary material online, *Table S2*). There was no

difference in the incidence of the secondary endpoints between the two groups (hazard ratio 1.0, 95% confidence interval 0.19–5.2, $P = 1.0$ vs. control).

Discussion

The major findings of the present study were that (1) the issue of DES-induced coronary hyperconstricting responses still exists even in the era of EES, the current standard second-generation DES, especially at the distal segment adjacent to the stent, (2) treatment with long-acting nifedipine suppressed the EES-induced coronary hyperconstricting responses, and (3) systemic inflammatory profiles were improved by long-acting nifedipine, which may be involved in the beneficial effects of the CCB. To the best of our knowledge, this is the first study demonstrating that chronic treatment with long-acting nifedipine could ameliorate coronary vasomotion abnormalities induced by the second-generation DES in humans.

Abnormal coronary vasoconstricting responses induced by the second-generation DES

The first-generation DES, such as SES and PES, have dramatically reduced the risk of ISR and have already been implanted in millions of patients in the world.[1] However, it was repeatedly shown that both SES and PES have the drawback of long-term durable polymer residues due to their non-biocompatible nature, causing the delayed structural[17] and functional healing[3,6,18] at the stented coronary segments with resultant LST and impaired coronary vasomotion.[19] Thus, the second-generation DES have been developed with biocompatible and bioabsorbance polymers.[20] Everolimus-eluting stent is currently the most widely used second-generation DES with biocompatible fluoropolymer and has been demonstrated to reduce adverse cardiac events including LST, non-fatal MI, and cardiac death compared with the first-generation DES, while maintaining similar inhibitory effects on ISR as the first-generation DES.[9] However, the information regarding the effect of EES on coronary vasomotion is limited, although it is widely used in the world.[21] Importantly, in the present study, the control group showed enhanced coronary vasoconstricting response to ACh with an average extent of 40%, which was similar to that observed with SES in our previous study.[6] This result suggests that DES-induced abnormal coronary vasomotion still remains unsolved even in the current era with the second-generation DES.

Beneficial effects of long-acting nifedipine on DES-induced abnormal coronary vasomotion

In the present study, nifedipine was stopped at least 48 h before follow-up CAG. Although we did not directly measure plasma level of nifedipine, our previous animal study demonstrated that plasma level of nifedipine was negligible at 24 h after discontinuation.[14] Also, it was reported that accumulation of nifedipine in the aorta or femoral artery was >0.02 μg/g-tissue, 1 day after discontinuation.[22] Thus, it is highly possible that residual nifedipine concentration in the stented coronary artery was negligible. Taken together, the beneficial effects of long-acting nifedipine observed in the present study were not related to its direct inhibitory effects against coronary vasoconstriction but were mediated by its indirect vasculoprotective effects. In the present study, the hyperconstricting response to ACh at the distal edge to EES and the inhibitory effects of long-acting nifedipine tended to be more pronounced in LAD than in LCX. It is conceivable that the difference in the number of cases between LAD and LCX could account for the difference in the results.

Possible mechanisms for the inhibitory effects of long-acting nifedipine on EES-induced coronary hyperconstricting responses

We have previously reported that inflammatory responses and thrombus formation are accelerated at the DES site of coronary arteries through activation of Rho-kinase.[5] The Rho/Rho-kinase pathway plays a central role in the molecular mechanism of coronary spasm through vascular smooth muscle cell hyperconstriction and the expression of Rho-kinase itself is increased by inflammatory stimuli in a positive manner.[8] Thus, it is conceivable that DES-induced inflammatory changes could enhance Rho-kinase activity with resultant coronary hyperconstricting responses.[5,6,8] In the present study, the hyperconstricting responses extended to the distal segment of the coronary artery from the stented site. We have recently demonstrated that the implantation of the first-generation DES, when compared with that of biolimus-eluting stent with bioabsorbable polymers, enhances adventitial vasa vasorum formation of the coronary artery and causes coronary hyperconstricting responses of the distal segment of the stent in pigs *in vivo*.[23] We consider that the same mechanism is involved in the case of EES implantation in humans as noted in the present study. Nifedipine has been shown to inhibit vascular inflammation through reduced production of pro-inflammatory cytokines and reactive oxygen species via peroxisome proliferator-activated receptor-gamma, and the resultant up-regulation of NO synthesis.[24–26] Moreover, we have recently demonstrated that chronic treatment with long-acting nifedipine could suppress excess inflammatory changes at the DES site and decrease Rho-kinase expression and activities in pigs *in vivo*.[14] In the present study, since it was difficult to evaluate the local inflammation at the DES sites technically in humans, we measured systemically serum hsCRP and plasma PTX3 levels as inflammatory markers and serum adiponectin level as an anti-inflammatory one.[15,16] The results showed that additional administration of long-acting nifedipine significantly lowered hsCRP level and increased adiponectin level. Altered serum levels of inflammatory markers, such as elevated hsCRP and low adiponectin levels, have been implicated in coronary vasomotion abnormalities in patient with VSA.[27] Furthermore, elevated serum hsCRP level was significantly associated with increased risks of adverse cardiac events, including stent thrombosis, death and MI in patients implanted with DES.[28] Taken together, the vasculoprotective effects of long-acting nifedpine are mediated, at least in part, by inhibition of inflammatory responses that could activate the Rho-kinase pathway in the coronary arteries.

Clinical implications

Cobalt-chromium EES is regarded as the current standard device for PCI. Additionally, the first- and second-generation DES including EES have already been implanted in millions of patients with CAD in the world, enhancing coronary vasoconstricting responses at the DES sites. It has been reported that impaired coronary vasomotor function is associated with increased cardiovascular risks.[29,30] A recent study in Germany demonstrated that enhanced coronary vasoconstrictions represent frequent cardiac causes for ongoing/recurrent angina in patients with previous PCI and no significant ISR.[31] Additionally, it was also noted that DES implantation could delay recovery of reperfusion-induced coronary vasomotor dysfunction and left ventricular dysfunction after AMI.[32] These findings suggest that coronary vasomotor dysfunction induced by DES is an important clinical issue that could affect quality of life and cardiac function of patients implanted with DES. Thus, we need to develop adjunctive medical treatments, like long-acting nifedipine as demonstrated in the present study, which could ameliorate DES-induced impairment of coronary vasomotor function.

Study limitations

Several limitations should be mentioned for the present study. First, the present study used Xience V® and Promus™ stents, commercially available in Japan during the enrolment period. Although EESs with new platforms are currently used, the drug-eluting system with durable polymers remains unchanged. Thus, our present findings should be applicable to the current clinical settings. Second, the information on the coronary vasomotor responses to ACh before and immediately after EES implantation was not available, since we did not perform ACh provocation tests before and immediately after stent implantation in the present study. However, no significant difference was found in vasomotor reactivity in the reference segment between the two groups. Third, several medications that could influence coronary vasomotion, such as statins, RASI, and β-blockers, were continued at the time of ACh test. However, the prescription rates of those were comparable between the two groups. Fourth, the high dropout rate of the randomized patients could influence the results of the present study. However, the ratio was confined to our assumption (25% dropout) and we finally analysed an adequate number of patients for evaluation of ACh provocation test. Additionally, as shown in Supplementary material online, *Table S3*, there was no difference in reasons for premature withdrawal and non-evaluability of the dropout patients between the two groups. Fifth, it is obvious that the sample size and the follow-up period of the present study were not enough to evaluate the impact of long-acting nifedipine on long-term prognosis of patients with EES. This point remains to be examined in future studies with a larger number of subjects and a longer follow-up period.

Conclusions

In the present study, we were able to demonstrate that DES-induced coronary vasomotion abnormalities still remains an important clinical issue even with the second-generation DES, for which long-acting nifedipine exerts beneficial effects associated with its anti-inflammatory effects in patients with CAD.

Authors' contributions

S.M., R.T. performed statistical analysis. H.S. handled funding and supervision. R.T., A.N., E.N., M.S., Y.Y., T.H., S.H., K.I., T.G., A.K., T.S., E.I. acquired the data. H.S., S.Y., J.T. conceived and designed the research.

H.S., J.T., R.T. drafted the manuscript. H.S. made critical revision of the manuscript for key intellectual content.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The authors thank all the members of the NOVEL Study investigators in each participating hospital. This study was supported in part by the grants-in-aid from the Ministry of Health, Labor, and Welfare and those from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Funding

This study was funded in part by Bayer Yakuhin Ltd. (Osaka, Japan) based on the research contract between the company and the Tohoku University Hospital. The company had no role in the study design, conduct of the study, data collection, data analysis, or preparation and submission of the manuscript.

Conflict of interest: H.S. has received lecture fees from Bayer Yakuhin Ltd (Osaka, Japan) and Daiichi Sankyo Co. Ltd. (Tokyo, Japan).

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