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Wall shear stress in the development of in-stent restenosis revisited. A critical review of clinical data on shear stress after intracoronary stent implantation

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Abstract

The average wall shear stress (WSS) is in 1 Pa range in coronary arteries, while the stretching effect of an implanted coronary stent can generate up to 3 × 10^5 times higher circumferential stress in the vessel wall. It is widely accepted that WSS plays a critical role in the development of restenosis after coronary stent implantation, but relevant clinical endpoint studies are lacking. Fluid dynamics modeling suggests an association between WSS and intimal hyperplasia, however, such an association is not established when the compensating healing process becomes an overshoot phenomenon. This review summarizes available clinical results and concepts of potential clinical importance. (Cardiol J 2016; 23, 4: 365–373)

Key words: wall shear stress, percutaneous coronary intervention, stent implantation, in-stent restenosis

Introduction

The coronary artery wall is exposed by two main loads: the frictional force of the blood flow and the blood pressure (BP). The flow results in wall shear stress (WSS) in tangential direction while BP acts perpendicular to the vessel wall and generates the circumferential stress according to the Laplace's law. The reported value of the physiological shear stress was approx. 1 Pa, while the circumferential stress was approx. 100–150 kPa assuming normal BP. In case of stent implantation in a narrowed coronary artery, further wall stress will be generated by the stent which can reach a value of 300 kPa, being 5 orders of magnitude higher than the flow-generated shear stress [1, 2].

There are several publications reporting follow-up data about the relation between WSS and the progression of the native coronary lesions following coronary stent implantation. It is generally accepted that endothelium is extremely sensitive to the WSS, producing anti-atherogenic substances (e.g., nitric oxide). Low and oscillatory shear stress conditions are pro-atherogenic and lead to atherosclerotic plaque formation [3–7].

The proposed mechanism involves mechanoreceptors in membrane of endothelial cells, e.g. receptor tyrosine kinase, such the vascular endothelial growth factor receptor (VEGFR) and adhesion molecules (such as platelet endothelial cell adhesion molecule [PECAM-1]). Shear stress also influences activation of endothelial cells through multiple mechanisms that target mitogen-activated protein kinases, nuclear factor-kappa-B, and endothelial nitric oxide synthase. Low shear stress can trigger intracellular cascades and shift phenotypic endothelial cell expression to an atherosclerotic prone state. Such endothelial cells display

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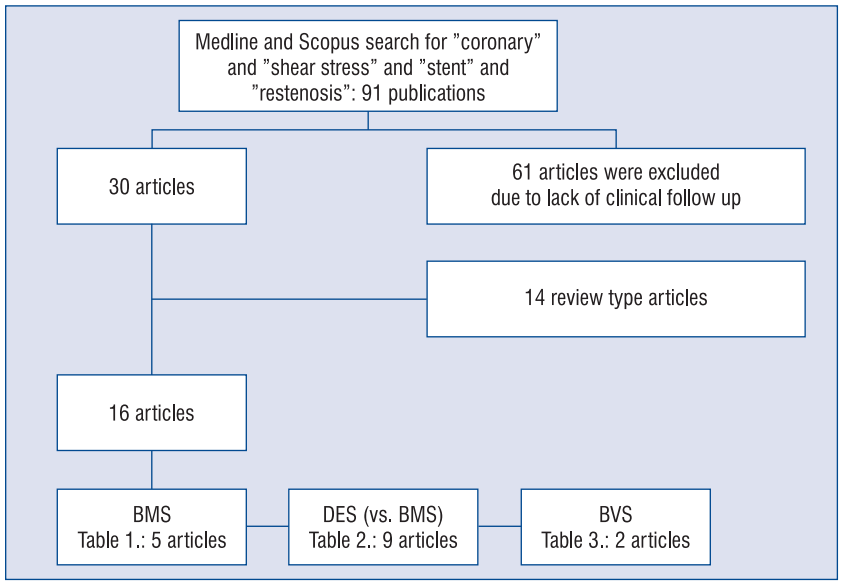

Figure 1. Flow chart of the selection of articles for review; BMS — bare metal stent; BVS — bioabsorbable vascular scaffold; DES — drug eluting stent.

enhanced expression of inflammatory molecules and higher rates of apoptosis [8–10].

According to already published data, the average WSS in coronary arteries during resting condition ranges from 0.5 Pa to 7 Pa and depends on the applied calculation method. Pathologically low WSS with values below 0.5–1 Pa has been reported to induce plaque formation. Besides the average WSS, it is also believed that the direction and oscillation of tangential friction also play a role in adverse intimal processes [11, 12].

Stent implantation results in acute mechanical damage to the vessel wall, initiating several platelet and inflammatory reactions. Later these processes lead to proliferation and migration of smooth muscle cells (SMCs) with accompanying formation of the extracellular matrix. In the case of standard re-endothelialization of the stented arterial segment, this healing process stops after the stent struts are covered with neointima, while an overshoot of the regeneration can progress to restenosis [13, 14].

In experimental models, shear stress clearly affects the migratory and proliferative responses of SMCs [15, 16]; clinical studies also indicate a correlation between intimal hyperplasia and low shear stress. However, data regarding systematic follow-up investigation and WSS calculation after stent implantation in large patient populations remain limited in number. This critical review summarizes the available data from human follow-up investigations and the proposed mechanisms underlying the effect of stent implantation on WSS, as well as the subsequent WSS-induced neointimal processes.

Methods

The main criteria for inclusion in this review were calculation of WSS in human coronary arteries and corresponding follow-up invasive investigation. PubMed and Scopus databases were searched for relevant articles published between January 1990 and October 2015 using a search strategy based on text words. The search string comprised "coronary", "shear stress", "stent", and "restenosis." The publications found were evaluated according to the involvement of human follow-up investigations. Articles not reporting repeated invasive assessment of stent implantation were rejected, as well as review articles not containing original observations. The remaining studies were classified according to the implanted stent type: bare-metal stent (BMS), drug-eluting stent (DES), or bioresorbable vascular scaffold (BVS) (Fig. 1).

Data were extracted and tabulated in a structured form showing parameters of the publications, number of observed patients, modality of coronary imaging, method of flow calculation, assumed flow, duration of follow-up, and main clinical findings (Tables 1–3).

Table 1. Studies on the follow-up of bare metal stent implantation and shear stress.

First author, journal, year of publication [reference]	Number of cases	Modality of coronary imaging	Method of flow calculation/software	Duration of follow up	Main clinical findings
Wentzel JJ, Circulation, 2001 [15]	14	ANGUS	Sepran software for mesh generation; it was assumed that 1.5 N/m^2, would be obtained by the entrance steady flow, at the outflow zero-stress conditions were applied; the Navier-Stokes equations were solved	6 months	NIH in Wallstents evaluated at 6-month follow-up after implantation are inversely related to the relative WSS distribution
Thury A, Images in Cardiovascular Medicine Circulation, 2002 [16]	1	ANGUS	Doppler flow and blood viscosity measurements were used as input conditions for application of computational fluid dynamics in the 3D reconstruction; the result were presented as a function of time over the cardiac cycle (pulsatile flow)	4 months later; both the angiogram and IVUS showed focal in-stent restenosis at the proximal edge of the stent at the site of the step-up	NIH was highest near the locations where average WSS was low; the temporal WSS pattern in the region of the step-up showed that the WSS vectors were retrogradely directed near the "corner" of the step-up
Stone PH, Circulation, 2003 [17]	6	IVUS images and biplane coronary angiography	The number of cine frames required for the opacified material to pass from the inlet of the section to the outlet was counted FCM (frame count method) (steady flow); the detailed intravascular flow characteristics were obtained by solving the transport Navier-Stokes equations	6 months	There was no difference in neointimal growth for the different shear stress regions within the BMSs
García J, J Biomec, 2006 [18]	7	IVUS images and biplane coronary angiography	Navier-Stokes equations; FLUENT (steady flow)	6 months	A negative correlation between the WSS and an increase in wall thickness was found
Papafaklis MI, Int J Cardiol, 2009 [19]	14 (7 patients were treated by vascular brachytherapy)	IVUS images and biplane coronary angiography	Navier-Stokes equations; steady flow was assumed at the inlet of the artery a to be 60 mL/min (ANSYS)	8 months	In-stent restenosis was inversely related to WSS after coronary artery stenting and vascular brachytherapy diminished the inverse relationship between neointima thickness and WSS

ANGUS — combined angiographic and intravascular ultrasound technique; ANSYS — commercial fluid dynamic modeling software; BMS — bare metal stent; 3D — 3-dimensional; FCM — frame count method; FLUENT — commercial fluid dynamic modeling software; IVUS — intravascular ultrasound; NIH — neointimal hyperplasia; WSS — wall shear stress

Table 2. Studies on the follow-up of drug eluting stent (vs. bare metal stent) implantation and shear stress.

First author, journal, year of publication [reference]	Number of cases	Modality of coronary imaging	Method of flow calculation/software	Duration of follow up, end-point	Main clinical findings
Van't Veer M, Eur Heart J, 2006 [20]	20 patients	Coronary angiograph; QCA	Pressure and Doppler flow wire were used to measure coronary pressure, velocity, average WSS and FFR (steady flow)	6 months	DES were physiologically superior to BMS
Suzuki N, Int J Cardiovasc Imaging, 2008 [21]	20 diabetic patients	Coronary angiography; IVUS	Navier-Stokes equations; FCM; ANSYS (steady flow)	9 months, no restenosis	WSS was not associated with NIH after implantation of DES or BMS in diabetic patients
Papafaklis MI, JACC Cardiovasc Interv, 2010 [22]	30 patients: 10 SES, 10 PES, 10 BMS	Coronary angiography; IVUS	Navier-Stokes equations; FCM; ANSYS (steady flow)	6 months, no restenosis	NIH is inversely correlated to WSS in PES as in BMS, but not in SES
Bourantas CV, Int J Cardiol, 2015 [23]	43 patients: 18 BMS, 25 DES	Coronary angiography; IVUS; IVUS-VH	Navier-Stokes equations; FCM; ANSYS (steady flow)	13 months, no restenosis	WSS determines neointimal formation in both BMS and DES and affects the composition of the neointimal in BMS
Papafaklis MI, Heart Vess, 2007 [24]	1 patients	Coronary angiography; IVUS	Navier-Stokes equations; FCM; ANSYS (steady flow)	10 weeks, no restenosis	NIH was found to be inversely related to WSS
Gijsen FJ, Am J Cardiol, 2003 [25]	6 patients	Coronary angiography; IVUS	Navier-Stokes equations; FCM; ANSYS (steady flow)	6 months, no restenosis	NIH 6 months after SES implantation was significantly related to WSS in 4 of the 6 patients studied
Hu ZY, J Interv Cardiol, 2010 [26]	11 patients with bifurcation lesions underwent crush stenting procedure	CAAS QCA 3D from bi- or monoplane X-ray coronary angiography imaging	An average steady velocity of 0.2 m/s was assumed; the numerical solution of steady Navier-Stokes equations were solved in STAR-CCM + + V4.04.011	After 8 months, there were 5 patients with restenosis	After a two-stent crush technique using DES, the degree of WSS reduction associated to the in-stent restenosis; a baseline low WSS, which decreased minimally after PCI, appeared to be the setting for restenosis
Zhang JJ, J Interv Cardiol, 2010 [27]	10 patients with bifurcations lesion underwent provisional stenting procedure with DES	CAAS QCA 3D from bi- or monoplane X-ray coronary angiography imaging	An average steady velocity of 0.2 m/s was assumed; the numerical solution of steady Navier-Stokes equations were solved in STAR-CCM + + V4.04.011	At the 8-month follow-up, there was no restenosis	Low endothelial WSS correlated with no restenosis in the main vessel, while a contradictory combination of high WSS and no restenosis was seen in the side branches after only POBA
Jenei C, Cor et Vasa, 2015 [28]	1 patient with DES	QCA software package (QAngio XA, Medis) for monoplane X-ray acquisitions	Pulsatile flow analysis by ANSYS CFX 15.0 software using the intracoronary pressure traces during a cardiac cycle	6 months, restenosis was found	Possibility that the extremely high WSS can also associate to restenosis at the distal edge of the stent

ANSYS — commercial fluid dynamic modeling software; BMS — bare metal stent; DES — drug-eluting stent; FCM — frame count method; FFR — fractional flow reserve IVUS — intravascular ultrasound; IVUS-VH — intravascular ultrasound-derived virtual histology; NIH — neointimal hyperplasia; PCI — percutaneous coronary intervention; PES — paclitaxed-eluting stent; POBA — plain old balloon angioplasty (without stent); SES — sirolimus-eluting stent; WSS — wall shear stress; CAAS QCA 3D — 3 dimensional Quantitative Coronary Analysis program of the Cardiovascular Angiographic Analysis System (Pie Medical Imaging); STAR-CCM — commercial fluid dynamic modeling software

Table 3. Studies on the follow-up of bioabsorbable vascular scaffold implantation and shear stress.

First author, journal, year of publication [reference]	Number of cases	Modality of coronary imaging	Method of flow calculation/ /software	Duration of follow up, clinical end-point	Main clinical findings
Papafaklis MI, EuroIntervention, 2013 [29]	1	Coronary angiography; IVUS; OCT	Navier-Stokes equations; FCM; ANSYS	6 months	The relationship between baseline WSS and 6-month neointimal thickness was much stronger in the OCT based 3D reconstruction than in the IVUS based calculation
Bourantas CV, JACC Cardiovasc Interv, 2014 [30]	12	Coronary angiography; OCT	Navier-Stokes equations; FCM; ANSYS	12 months	An inverse association between WSS and NIH was found after Absorb BVS implantation as a consequence of local hemodynamic milieu on vessel wall healing

ANSYS — commercial fluid dynamic modeling software; BVS — bioabsorbable vascular scaffold; 3D — 3-dimensional; FCM — frame count method; IVUS — intravascular ultrasound; NIH — neointimal hyperplasia; OCT — optical coherence tomography; WSS — wall shear stress

Results

Studies concerning the measurement of neointimal hyperplasia (NIH) during a follow-up investigation in relation to evaluation of the shear stress after BMS implantation are summarized in Table 1. Tables 2 and 3 report the available data regarding DES and BVS. It is clear from the "Modality of coronary imaging" columns that intravascular ultrasound (IVUS) was the most frequent tool for the detection of NIH for the BMS and DES studies, while optical coherence tomography was necessary for the appropriate assessment of BVS results. The methods for calculation usually assumed a steady flow, therefore an average of the WSS during the cardiac cycle was determined.

BMS studies

Wentzel et al. [15] published a human *in vivo* study of the effect of shear stress on NIH in 14 coronary arteries 6 months after a Wallstent implantation. The average relationship between neointimal thickness and shear stress was as follows: neointimal thickness = (0.59 ± 0.24) − (0.8 ± ± 0.10) × WSS [mm] ($p < 0.05$). The resulting data showed that neointimal growth occurs in regions of low shear stress [15].

In a case report, Thury et al. [16] also found the highest NIH at the locations where average WSS was low. He detected a focal in-stent restenosis with a step-up phenomenon at the proximal edge of the BMS. The temporal WSS pattern in the region of the step-up showed existence of a region of flow separation with oscillating WSS [16].

Stone et al. [17] found an increase in intima-media thickness, a decrease in lumen radius, and an increase in endothelial shear stress (ESS) at all levels of baseline ESS in 6 stented arteries, but there was no difference in neointimal growth for the different shear stress regions within the BMSs [17].

García et al. [18] also observed a negative correlation between the WSS and an increase in wall thickness on the mid-right coronary artery in 7 patients after BMS implantation.

Using coronary angiography and IVUS, Papafaklis et al. [19] performed 3-dimensional artery and stent reconstruction in 14 patients at an 8-month follow-up after BMS implantation with or without adjunctive beta-vascular brachytherapy. They found that in-stent restenosis was inversely related to WSS after coronary artery stenting and that vascular brachytherapy diminished the inverse relationship between neointima thickness and WSS. These authors also emphasized that WSS cannot predict the exact locations of NIH in all cases, since the thickening does not necessarily occur in all regions where WSS is low and not all regions where WSS is high are spared from NIH (Table 1).

DES studies

Van't Veer et al. [20] investigated physiological parameters at stent implantation and at a 6-month follow-up in 20 sirolimus-eluting stents (SES) and 20 BMSs. In this study, the SES were considered to produce a more physiologically hemodynamic performance 6 months after the procedure due to the fact that they maintained lower WSS values when compared with the BMSs. This concept contrasts with the findings of previous studies.

With the exception of the articles published by Suzuki et al. [21] and Papafaklis et al. [22], where the WSS was not associated with NIH after implantation of SES, further data on straight vessels confirmed that the WSS determines neointimal formation in DESs [23–25].

In the study by Suzuki et al. [21], there was no correlation between NIH and WSS in a diabetic population 9 months after 11 SES and 9 BMSs, while Papafaklis et al. [22] demonstrated a significant inverse NIH to WSS relation in only 3 of 10 SES patients with an overall nonsignificant correlation 6 months after SES implantation. The explanation of the results of the previous study proposed the role of diabetes (it may amplify the NIH response), while both studies concluded that sirolimus can attenuate effectively the low WSS induced vascular cell migration and proliferation.

With regard to bifurcation lesions, in the same issue of the "Journal of Interventional Cardiology", Hu et al. [26] and Zhang et al. [27] demonstrated that DES implantation with a crush technique or provisional technique was associated with restenosis in the main branch and the degree of WSS reduction, i.e., with an immediate decrease of the WSS after stenting, but without achieving a low WSS. A baseline low WSS, which decreases minimally after percutaneous coronary intervention and recovers to its approximate baseline level, appeared to be the setting for restenosis. These authors concluded that the mechanism of prevention of restenosis in the side branch in the case of provisional stenting (without side-branch stent) works by increasing the WSS, while in the main branch, the mechanism of prevention of restenosis is secondary to drug elution. A case report has recently been published of restenosis in a straight vessel segment with a very high shear stress near the site of step-down phenomenon [28], raising the possibility of extremely high WSS being associated with restenosis at the distal edge of the DES (Table 2).

BVS studies

Investigating the effect of WSS on NIH after BVS implantation [29], the relationship between baseline WSS and 6-month neointimal thickness was much stronger in the optical coherence tomography-based, 3-dimensional reconstruction than in the IVUS-based calculation. In another BVS study, an inverse association between WSS and NIH was also conferred as a consequence of local hemodynamic milieu on vessel wall healing (Table 3) [30].

The majority of publications summarized in Tables 1–3 favor the concept that low and oscillating shear stress is associated with intimal hyperplasia, but provide conflicting data regarding the clinical endpoints. Observations on the relationship between clinical restenosis requiring revascularization and WSS are restricted to only 2 studies of bifurcation lesions and 2 case reports of straight vessel segments, which also reach opposite conclusions. In all other papers reviewed, intimal hyperplasia was used as a surrogate endpoint and not as a clinical one.

Discussion

While shear stress is applied mainly to the endothelium in native coronary arteries [31], after endothelial injury caused by the stent implantation the most important mechanosensing cells are the SMCs. An early experimental study by Sterpetti et al. [32] reports that vascular SMCs may sense shear stress and it directly inhibits their proliferation. Shear stress affects the migratory and proliferative responses of vascular SMCs via several pathways, and can be transformed from a contractile to synthetic phenotype [33, 34].

The average WSS is considered only approx. 1 Pa in coronary arteries, while the stretching effect of an implanted coronary stent can generate up to 3×10^5 times higher circumferential stress in the vessel wall (Fig. 2) [35].

According to the established mechanism described above, it is clear that fluid shear stress delivers mechanosignal transduction that leads to initiation of neointimal growth, but also circumferential stress induced by the stretching effect of the implanted stents, being much higher in magnitude, can play an important role in the stimulation of the phenotypic adaptation to a dedifferentiated synthetic state of SMCs. Although the

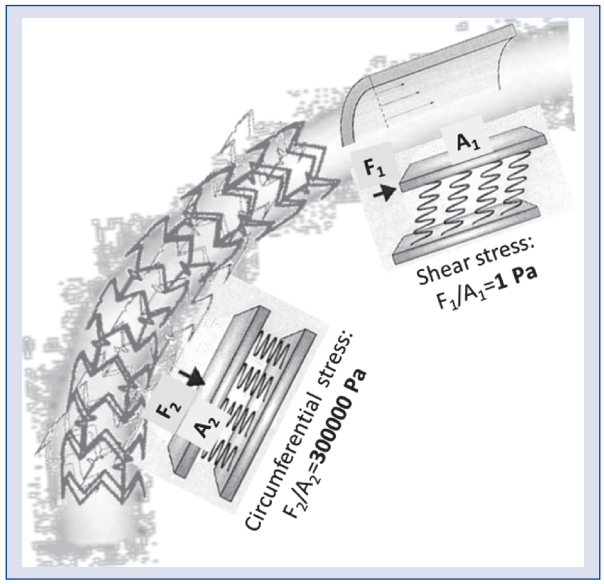

Figure 2. Fluid shear stress vs. circumferential wall stress: the flow results in wall shear stress in tangential direction. In the case of stent implantation to a narrowed coronary artery, wall stress will be generated by the stent which can reach a value of 300 kPa, being 5 orders of magnitude higher than the flow-generated shear stress.

mechanisms controlling the response of SMCs to mechanical stress have not been fully clarified, it seems that mechanical stretch is transmitted to the SMCs through macromolecular protein complexes, such as transmembrane integrins binding with intracellular adaptors (e.g., paxillin and vinculin) and signaling proteins (focal adhesion kinases) [36–38]. Macroscopically, stent placement induces straightening of arterial segments, slightly altering the distribution of shear stress. Microscopically, the local shear stress is mainly determined by the height of stent struts. A stent that protrudes into the lumen will alter the coronary flow, leading to changes in local shear stress distribution [39].

It is also crucial to comprehend that the newly regenerated endothelial layer is often dysfunctional [40]. This fact can play a key role in the restenotic process, when the uncontrolled neointimal formation is not stopped after the shear stress-induced "normal" re-endothelialization increased the flow velocity by decreasing the lumen diameter. In this case, the "autoregulation" is definitively destroyed and the exact mechanism responsible for the overshoot of the neointimal proliferation remains to be clarified.

However, restoration of the original geometry by stent implantation could theoretically re-establish the original WSS conditions that promoted *de novo* atherosclerosis formation. This mechanism does not seem obvious in the early restenotic process, but cannot be excluded in the background of late in-stent neoatherosclerosis.

Further technical issue in WSS calculation has arisen recently with regard to the modeling of side branches. As demonstrated by Li et al. [41], the average WSS was 4.64 Pa lower in the cases when side branches were taken into account than in the traditional straight vessel model. The studies cited in this review all used straight vessel segment calculation for the 3-dimensional reconstruction, therefore in the cases of pressure-based calculation they are hampered by this type of limitation.

The reviewed papers calculated the average shear stress inside the stented lumen rather than the microenvironment at the struts of the stents, therefore the ignorance of the stent reconstruction also could form an error source for the exact local shear stress calculation inside the stents. The right methodology would be to reconstruct both the lumen and the implanted stent, and use them both in the WSS calculation.

The complex relation between the flow shear stress and the restenotic process after stent implantation contributes to the difficulties of conducting observational studies. The follow-up intravascular imaging at a special time point could not provide right information about the whole process because the further prognosis usually could not be predicted on the basis of the investigation. Furthermore, the calculated shear stress is dependent on the applied boundary conditions, which are not patient-specifically incorporated in the modeling. The calculation show quite a wide range of shear stress (with a broad intermediate range) as in healthy vessels. This fact could limit the correlation of the shear stress with the observed intimal hyperplasia.

Summary and future perspectives

While the significance of WSS after stent implantation has been proved in neointimal formation, clinical restenosis endpoints are lacking. The lack of large-scale clinical endpoint studies is surprising, as there is a high number of well-controlled follow-up studies regarding the clinical results of different types of stent implantations, which theoretically can be evaluated even ret-

rospectively using appropriate WSS assessment methods.

An adequately large number of patients is required to determine confounder-adjusted estimates. Longitudinal prospective studies after stent implantation with shear stress evaluation are also required for exploring deeper inside of the restenotic pathophysiology.

The available data raise the question of whether the detected NIH is a part of the healing process after stent implantation or a predictor of later clinical restenosis. Numerous other questions need to be answered for further research. Regarding WSS modeling, it is not clear at present whether an assumption of non-pulsatile steady flow provides enough information about the mechanism of restenosis after stent implantation. Even when the cyclic variation of the pulsatile flow is incorporated, it is still questionable whether we can analyze the flow alone without the stress and strain of a much higher magnitude inside the vessel wall as a consequence of the radial stretching of the implanted stent [42]. The rapid development of computational fluid dynamics methods provides a promise to elucidate the role of hemodynamic forces in the pathological processes of the formation of exaggerated intimal thickness after stent implantation.

Conflict of interest: None declared

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