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Therapeutic Potential of Oral Antiproliferative Agents in the Prevention of Coronary Restenosis

Pramod Kuchulakanti and *Ron Waksman*

Division of Cardiology, Washington Hospital Center, Washington, DC, USA

Abstract

The treatment of coronary artery disease has reached many milestones – from balloon angioplasty to drug-eluting stents. The last decade witnessed the revolution of bare metal stents with new designs, alloys and strut thicknesses. Yet restenosis, the aphorismic 'Achilles heel', remains to be conquered. The restenosis rates with balloon angioplasty alone are 30–40% and are reduced to 20–30% with stents. Although intravascular brachytherapy proved to be a durable and safely used technique to treat in-stent restenosis, clinical event rates were not reduced to single digits.

Drug-eluting stents are showing positive results in this direction, but it is too early to predict their efficacy in various subsets of lesions. With the increased usage of these stents, there are reports of problems such as late stent malapposition, subacute and late thromboses, and aneurysm formations due to the vessel toxicity associated with this method of treatment. Furthermore, when multivessel stenting is considered, the cost of drug-eluting stents is a significant problem given the fact that these are no longer 'zero restenosis' devices.

There is a definite need for a simple, safe and durable solution to restenosis. Oral agents are an alternative delivery strategy that can target multiple coronary lesions, which are targets for catheter-based revascularisation with any approved metal stent and with potentially lower cost. Although oral agents have been an interesting option to treat restenosis and several agents have been tested in trials since the 1980s, the results were disappointing.

The development of devices such as intravascular ultrasound has led to a greater understanding of restenosis mechanisms, and the focus on pathophysiological mechanisms, which centred mainly on platelets, growth factors and lipids, has changed to inflammation, endothelium and smooth muscle cell proliferation.

Accordingly, the targets of pharmaceutical agents have shifted from platelets to cell cycle inhibition, smooth muscle cell proliferation and migration, synthesis of extra cellular matrix, and inflammatory mediators. Initial encouraging results with oral drugs such as cilostazol, sirolimus (rapamycin) and thiazolidinediones indicate a definite place for this strategy to reduce restenosis. A desirable oral agent would be anti-inflammatory, inhibit smooth muscle cell migration and proliferation, promote endothelial growth, and be well tolerated and free from significant adverse effects. It may be useful to start with a high loading dose before stent implantation and then follow with a short-term lower maintenance

dose. Future trials should be aimed at finding an ideal agent, effective loading dose, maintenance dose and optimum duration of therapy.

The introduction of balloon angioplasty to treat coronary atherosclerosis has created a difficult problem, namely restenosis. The interventional cardiology community, and pharmaceutical and device industries are sparing no efforts to combat this problem, which continues to be a formidable challenge. Coronary stents have reduced its incidence to 20–30%, a reduction of 30–40%.[1,2] The recent development of drug-eluting stents has further decreased, but not eliminated, the problem.[3] Therefore, efforts to overcome the challenge of restenosis – including research into newer mechanisms, targets, experimental and therapeutic agents, and clinical trials – are still actively pursued. This article discusses the oral agents tested in this area, trials conducted thus far and their results, and the limitations of and future directions for this modality of treatment.

1. Why Oral Agents for Restenosis?

The simplest reason for the use of oral agents for restenosis is ease of administration. More importantly, there are several limitations to local delivery of drugs in the form of drug-eluting stents. The efficacy of these new devices depends on several variables, including the selection of an effective drug, its solubility, diffusion characteristics, release kinetics, arterial tissue concentration and retention, and whether the platform is polymer based or nonpolymeric. Local delivery of the drug in this manner may delay rather than prevent neointimal growth. This is supported by preclinical studies that show impaired healing and neointimal catch-up.[4] There is concern that neointimal growth will accelerate in response to the nonbiodegradable polymer coating after complete elution of the drug. These issues may rejuvenate investigations into systemic therapy, particularly with those agents that have shown positive results when administered locally, as standalone therapy or as an adjunct to drug-eluting stents. Other reasons include the possibility of administering oral agents over a longer period of time in patients with multiple stent implantations; the ability to withdraw the drug in case of hypersensitivity or intolerance; and perhaps the lack of effects, such as subacute thrombosis, aneurysm formation and the like, associated with drug-eluting stents.

2. Pathology of Restenosis and Targets for Prevention

Atherosclerosis is a progressive, inflammatory condition of the vessel wall leading to accumulation of lipid and other materials causing lesion formation and lumen encroachment.[5] Balloon angioplasty fractures these lesions and helps re-establish the lumen patency. Stents act as scaffolding and prevent elastic recoil and vascular remodelling.[6,7] Although stents are effective in reducing restenosis by eliminating these two mechanisms, they cause restenosis by neointimal hyperplasia. Stents are associated with a prolonged, intense inflammatory state with recruitment of leucocytes, mainly monocytes. The initial events immediately after stent placement result in de-endothelialisation and the deposition of a layer of platelets and fibrin at the injured site. Activated platelets express adhesion molecules such as P-selectin and glycoprotein (GP) Ibα, which attach to circulating leucocytes via platelet receptors. Under the influence of cytokines, leucocytes bind tightly to adhesion molecules via direct attachment to platelet receptors such as GPIbα. Cytokines released from vascular smooth muscle cells (VSMCs) and resident leucocytes induce migration of leucocytes across the platelet-fibrin layer and into the tissue. Growth factors are released from platelets, leucocytes and VSMCs, and influence the proliferation and migration of VSMCs from the media into the denuded intimal area. The cell cycle consists of resting phase, G_0, G_1, S phase and M phase. Once stimulated, the cell undergoes these phases and proliferates. The resultant neointima consists of VSMCs, extracellular matrix and macrophages re-

cruited over several weeks. There is a shift toward fewer cellular elements with greater production of extracellular matrix followed by re-endothelialisation of at least part of the injured vessel surface over time. The difference between restenosis that occurs as a result of balloon angioplasty and that from stent implantation is mainly due to a longer duration and more intense inflammatory response with stents. Therefore, it is intriguing to assume that targeting the release of these mediators, the inhibition of cell cycle and migration of VSMCs would reduce neointimal proliferation.

Studies in the last two decades have investigated several oral agents for their efficacy in decreasing restenosis, but only a few of them reported beneficial effects.[8,9] Table I lists the drugs that failed to show consistent benefit in reducing restenosis. While radiation therapy was successful in reducing in-stent restenosis, it failed to obtain a single-digit restenosis rate for *de novo* lesions, especially when coupled with stents, either as a platform of the radioactive stent or a catheter-based system. Nevertheless, the experimental work with vascular brachytherapy guided the direction for prevention of restenosis. The work focused primarily on antiproliferative therapy and intervention in the cell cycle. On the basis of current understanding of the mechanism of restenosis, the pharmacological agents useful to treat restenosis are grouped into five classes: (i) anti-inflammatory and immunomodulators; (ii) antiproliferative agents; (iii) inhibitors of VSMC migration; (iv) agents promoting re-endothelialisation; and (v) vitamins, antioxidants and others.

Table I. Oral agents that failed to reduce restenosis in clinical trials

Antiplatelet and antithrombotic drugs
Aspirin (acetylsalicylic acid), dipyridamole, ticlopidine
Thromboxane A_2 antagonists: vapiprost and sulotroban
Omega-3 fatty acids
Warfarin
Antiallergic drugs
Tranilast
Growth factor antagonist
Trapidil
ACE inhibitors: cilazapril, fosinopril, enalapril
Nitric oxide donors
Molsidomine
Antifibrotic drugs
Colchicine
HMG-CoA reductase inhibitors
Lovastatin, fluvastatin, simvastatin
Vitamins
Tocopherol
Serotonin receptor antagonist
Ketanserin
Antianginal agents
Calcium channel antagonists and β-adrenoceptor antagonists

Some of these agents have more than one action. For example, sirolimus (rapamycin) is antiproliferative, but also carries anti-inflammatory properties and possesses immunoregulatory functions. Similarly, cilostazol has antiplatelet activity, but also inhibits VSMC migration and directly inhibits intimal proliferation. Table II lists the drugs that have shown positive results in clinical trials and their mechanisms of action.

2.1 Anti-inflammatory Agents and Immunomodulators

Oral agents in this category include corticosteroids, NSAIDs, HMG-CoA reductase inhibitors (statins) and tranilast.

2.1.1 Corticosteroids

Corticosteroids are potent anti-inflammatory agents, which also have immunosuppressive activity. Interleukin (IL)-1 and IL-6, secreted by activated macrophages, are powerful stimuli for VSMC proliferation and hepatocyte-stimulating factors inducing the production of acute-phase proteins, including C-reactive protein (CRP). Accordingly, preprocedural high plasma levels of CRP and a persistent elevation of plasma CRP levels after successful stent implantation have been found to predict the risk of restenosis.[28,29] In a double-blind, randomised, placebo-controlled study, Versaci et al.[10] investigated the effect of oral prednisone on the angiographic restenosis rate after successful stent implantation in patients with persistent elevation of systemic markers of inflammation after the procedure. Eighty-three patients who underwent successful stenting with CRP levels >0.5 mg/dL 72 hours after the procedure were randomised to receive oral

Table II. Oral agents to treat coronary restenosis and the trials conducted

Oral agent	Principal mechanism of action	Trial	Results
Prednisolone	Anti-inflammatory	IMPRESS[10]	Significantly low restenosis and late loss
Pravastatin	Anti-inflammatory	REGRESS[11]	Lower binary restenosis at 2 years
Tranilast	Inhibits VSMC migration and proliferation, decreases collagen synthesis	TREAT-1[12] TREAT-2[13] PRESTO[14]	Lower restenosis Lower restenosis No difference
Sirolimus (rapamycin)	Inhibition of CDK complexes, antiproliferative	ORAR[15]	Lower restenosis
		ORBIT (unpublished data)	Lower restenosis
Thiazolidinediones	Inhibitory action on VSMC growth, migration and suppression of neointimal proliferation	Takagi et al.[16] (troglitazone) Takagi et al.[17] (pioglitazone)	Reduced neointimal proliferation Reduced restenosis, TLR and neointimal proliferation
Cilostazol	Inhibitory effect on VSMC migration by inhibiting P-selectin release	ESPRIT[18] Kimishirado et al.[19] CREST[20]	Low restenosis Low restenosis and TLR Low restenosis
Folic acid	Reduction in plasma homocysteine levels	Swiss Heart Study[21]	Reduced TLR
Probucol	Antioxidant	MVT and Probucol Study Group[22]	Low restenosis
		PART[23]	Low TLR
		CART[24]	Less neointimal proliferation
Pemirolast	Inhibition of VSMC proliferation and migration	Ohsawa et al.[25]	Low restenosis and neointimal hyperplasia
Sarpogrelate	Inhibits serotonin induced VSMC proliferation	Fujita et al.[26]	Low restenosis
Valsartan	AT-II receptor antagonist, improved endothelial function	VAL-PREST[27]	Low restenosis and re-intervention

AT = angiotensin; **CART** = Canadian Antioxidant Restenosis Trial; **CDK** = cyclin-dependent kinase; **CREST** = Cilostazol for Restenosis Trial; **ESPRIT** = Eliminiation of restenosis after Stenting following Plaque Reduction with platelet Inhibitor Trial; **IMPRESS** = Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation Study; **MVT** = Multivitamins; **ORAR** = Oral Rapamycin to prevent Restenosis – Argentina Single-Center Study; **ORBIT** = Oral Rapamycin to Inhibit Restenosis Trial; **PART** = Probucol Angioplasty Restenosis Trial; **PRESTO** = Prevention of Restenosis with Tranilast and its Outcomes; **REGRESS** = Regression Growth Evaluation Statin Study; **TLR** = Target Lesion Revascularisation; **TREAT** = Tranilast Restenosis Following Angioplasty Trial; **VAL-PREST** = Valsartan for Prevention of Restenosis after Stenting; **VSMC** = vascular smooth muscle cells.

prednisone or placebo for 45 days. The 6-month restenosis rate and late luminal loss were lower in the prednisone-treated patients than in the placebo recipients (7% vs 33%, $p = 0.001$, and 0.39 ± 0.6mm vs 0.85 ± 0.6mm, $p = 0.001$, respectively).

Three other randomised, placebo-controlled studies[30-32] investigated the influence of intravenous methylprednisolone before angioplasty with negative results. In these studies, methylprednisolone 1g was infused intravenously 2–24 hours before planned percutaneous transluminal coronary angioplasty (PTCA) and stenting. In M-HEART (Multi-Hospital Eastern Atlantic Restenosis Trial),[31] the infused methylprednisolone was followed by oral prednisolone 60 mg/day for 1 week. Angiographic restudy in M-HEART showed restenosis rates of 36% versus 40%, 40% versus 39%, and 17.5% versus 18.8% (not significant) compared with placebo, in these three studies, respectively.[30-32] It is not surprising that these trials failed to show any benefit because restenosis is a slow and chronic inflammatory process, and a single pulse dose of methylprednisolone would not provide a durable effect.

2.1.2 NSAIDs

The proposed mechanism of action of NSAIDs includes inhibition of prostaglandin synthesis in inflammatory cells, thus blocking monocyte adhesion, cell differentiation, proliferation and angiogenesis.[33] Although it is theoretically appealing to consider NSAIDs, which reduce restenosis by interfer-

ing with the release of inflammatory substances, thus impairing migration of monocytes, data from animal experiments did not translate into clinical reality. Ebselen, a selenium-containing NSAID with additional antioxidant properties, was tested in 80 patients undergoing PTCA and was shown to be associated with lower restenosis compared with placebo (18.6% vs 38.2%, $p < 0.05$).[9] However, experimental data in animals showed sulindac to be beneficial in reducing stenosis, but aspirin (acetylsalicylic acid) failed to show any benefit. This could be as a result of the inability of aspirin to inhibit cyclo-oxygenase (COX)-2. Furthermore, sulindac has additional actions independent of COX activity, such as inhibition of proliferation, induction of apoptosis, inhibition of peroxisome proliferator-activated receptor (PPAR)-δ and increased formation of intracellular ceramide leading to the induction of apoptosis. These mechanisms have been postulated for other NSAIDs such as aspirin and for the new specific COX-2 inhibitors as well. The main reasons NSAIDs have not been tested in clinical trials are toxicity issues and the very high doses required to achieve these effects *in vivo*.

2.1.3 HMG-CoA Reductase Inhibitors (Statins)

Clinical efficacy of the anti-inflammatory properties of statins has been shown in several trials independent of their lipid-lowering effects.[34,35] Statins reduce CRP levels and it is known that elevated CRP levels are associated with restenosis. However, counter intuitively, several trials that tested statins for restenosis prevention were disappointing.[36-39] The only trial that showed reduction in restenosis was REGRESS (Regression Growth Evaluation Statin Study),[11] which used pravastatin 40mg once daily for a period of 2 years, as opposed to other trials which assessed restenosis within 6 months. In this study, the binary restenosis assessed at 2 years was significantly lower in the pravastatin group compared with pravastatin 40mg once a day. Importantly, stents were not used in this trial and positive remodelling at the end of 2 years may have contributed to better results. Overall, the ability of statins to prevent restenosis remains unproven.

2.1.4 Tranilast

The antiallergy drug tranilast is a derivative of anthranilic acid. Tranilast interferes with proliferation and migration of VSMCs, and also suppresses collagen synthesis in VSMCs. Whereas TREAT (Tranilast Restenosis Following Angioplasty Trials) 1 and 2[12,13] reported a reduction in restenosis, the large-scale multicentre, double-blind, randomised, placebo-controlled PRESTO (Prevention of Restenosis with Tranilast and its Outcomes) trial did not find any significant differences between tranilast and placebo.[14]

2.2 Antiproliferative Drugs

Two different strategies to control neointimal proliferation after vascular injury have been proposed. First is the cytostatic approach, which aims to control the regulation and expression of cell cycle-modulating proteins at any level along the pathway modulating cell proliferation. Secondly, the cytotoxic approach – killing proliferating cells – has the disadvantage of inducing necrosis, which may contribute to weakening of the vessel wall. Among the antiproliferative agents proposed for this application are sirolimus and its analogue everolimus, and a variety of antineoplastic drugs such as dactinomycin (actinomycin D), vincristine, doxorubicin and vinblastine.

2.2.1 Sirolimus (Rapamycin)

The natural macrocyclic lactone sirolimus is a potent immunosuppressive agent. It was developed by Wyeth-Ayerst Laboratories (Philadelphia, PA, USA) and approved by the US FDA for the prophylaxis of renal transplant rejection in 1999.[40,41] Sirolimus has its roots in Easter Island, where an actinomycete *Streptomyces hygroscopicus* was found that produced a novel macrolide antibiotic with potent antibacterial, antifungal, immunosuppressive and antimitotic activities.

Sirolimus binds to an intracellular receptor protein and elevates p27 levels, which leads to inhibition of cyclin-dependent kinase complexes and ultimately induces cell-cycle arrest in the late G_1 phase. It inhibits proliferation of both rat and human VSMCs *in vitro* and reduces intimal thickening in

models of vascular injury.[41,42] Sirolimus inhibits T-cell activation and proliferation, which occurs in response to antigenic and cytokine stimulation; however, its mechanism is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK binding protein-12, to generate an immunosuppressive complex. This complex binds to and inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the phase progression of the cell cycle.[42,43]

Oral sirolimus is absorbed rapidly and blood concentrations peak within 1 hour. A loading dose three times the maintenance dose will achieve steady-state concentrations within 24 hours in most patients. The drug is metabolised by the cytochrome P450 (CYP) system and is well tolerated. Rodriguez et al.[15] reported the results of the ORAR (Oral Rapamycin to Prevent Restenosis – Argentina Single-Center) trial in which 34 patients undergoing coronary stent therapy received oral sirolimus (6mg loading dose, followed by 2 mg/day) for 1 month after stent implantation for *de novo* and restenotic lesions. At 6 months, angiography showed a restenosis rate of 18.9% in *de novo* lesions and 50% in in-stent restenotic lesions. Interestingly, it was found that restenosis was 0% in patients with sirolimus concentrations >8 μg/mL. Another trial involving 22 patients examined the same regimen of sirolimus for in-stent restenosis and reported very unfavourable results: high recurrent restenosis (86.7%) and discontinuation of the study drug (50%).[44]

ORBIT (Oral Rapamycin to Inhibit Restenosis Trial) was conducted at our institution, the Washington Hospital Center (Washington, DC, USA), and divided 60 patients into two groups of 30 according to a maintenance dose of sirolimus 2 or 5mg. Six-month angiographic restenosis was 6.9% in the 2mg group and 7.1% in the 5mg group. In this study, 27 of the 30 patients completed the 4-week course in the 2mg group, but one-third (10 of 30) of the patients in the 5mg group did not complete the course.[45] Adverse effects were reported in 13 of 30 patients (43.3%) in the 2mg group and 20 of 30 (66.7%) in the 5mg group (unpublished data). ORBIT-II is an international, multicentre trial investigating the efficacy of oral sirolimus to inhibit restenosis in patients with bare metal stents.

2.2.2 Sirolimus Analogues and Anti-immunosuppressive Molecules

The initial success with sirolimus has led to the search for sirolimus analogues. Among these are everolimus (a new macrocyclic triene derivative), ABT 578 and other anti-immunosuppressive compounds such as mycophenolic acid, ciclosporin (cyclosporine) and tacrolimus, which inhibit proliferation via G_1 arrest and reduce the immune response. Data from animal experiments suggest that oral everolimus administered for 1 month effectively inhibits neointimal hyperplasia;[46] however, human trials are yet to be undertaken.

2.2.3 Thiazolidinediones

Thiazolidinediones are a class of antidiabetic drugs known to have inhibitory action on VSMC growth, migration and suppression of neointimal proliferation.[47,48] Thiazolidinediones include rosiglitazone, troglitazone and pioglitazone. Troglitazone and pioglitazone were tested in two separate studies involving patients with type 2 diabetes mellitus following coronary stent implantation and were shown to inhibit neointimal hyperplasia by serial intravascular ultrasound scanning study.[16,17] Accumulating evidence shows that this group of compounds reduces markers of endothelial cell activation and levels of CRP and fibrinogen even in coronary artery disease patients without diabetes.[49] Thus, these agents may be useful in treating restenosis in both diabetic and non-diabetic patients. Further studies with a larger number of patients may prove the efficacy of this group of drugs.

2.3 Inhibitors of Smooth Muscle Cell Migration

2.3.1 Cilostazol

As mentioned in section 2, cell activation and cell-to-cell interaction of platelets and leucocytes

mediated by adhesion molecules are considered to be important for VSMC proliferation after coronary angioplasty. Coronary stenting produces the release of an adhesion molecule, P-selectin, from α-granules of activated platelets. P-selectin-mediated platelet-leucocyte interaction has a crucial role in the development of stent restenosis. Cilostazol is an antiplatelet, antithrombotic, phosphodiesterase III inhibitor that, by inhibiting P-selectin release, has inhibitory effects on VSMC migration. In addition, cilostazol may act directly to inhibit intimal hyperplasia.

Randomised trials conducted with cilostazol 200 mg/day have shown that it is effective in reducing restenosis.[18-20] The randomised, double-blind, placebo-controlled CREST (Cilostazol for Restenosis Trial) involved 705 patients who underwent successful coronary stent implantation and received the study drug for 6 months (placebo or cilostazol 100mg twice daily). It showed a significant reduction in binary restenosis (>50% diameter stenosis) in the cilostazol group compared with placebo (20.88% vs 34.59%; p = 0.0006), a 39.5% relative risk reduction. Subgroup analysis revealed less restenosis in diabetic patients (16.95% vs 36.99%; p = 0.01) and in vessels <3mm (21.93% vs 34.38%; p = 0.007).[19]

2.4 Strategies to Promote Healing and Re-endothelialisation

In contrast to the agents outlined earlier in this section that primarily inhibit biological activity, a strategy to promote healing and re-endothelialisation may indirectly reduce the trigger for proliferation and inflammation by rapidly restoring the injured endothelium and its functions. A number of studies have shown the role of endothelial growth factors (EGF), fibroblast growth factors and vascular EGF in modulating the re-endothelialisation process.[50-52] However, there are no oral formulations to test this strategy with as yet.

2.5 Vitamins, Antioxidants and Other Agents

There have been claims that other drugs can potentially enhance healing and minimise the neointimal formation by various mechanisms. These include antioxidants with vitamins,[21] probucol,[22-24] the antipruritic agent pemirolast,[25] the serotonin receptor antagonist sarpogrelate[26] and the angiotensin-I receptor antagonist valsartan.[27] Although individual trials failed to show any benefit, meta-analyses of calcium channel antagonists[53] and β-adrenoceptor antagonists[54] showed reduction in angiographic and clinical restenosis.

With calcium channel antagonists, there was a 14.3% reduction in angiographic restenosis and a 31.0% reduction in combined endpoint of death, myocardial infarction and revascularisation.[53] With β-adrenoceptor antagonists, there was a 23.5% reduction in 6-month target lesion restenosis and a 23.7% reduction in 9-month clinical restenosis.[54]

3. Limitations of Studies with Oral Agents

Table III summarises the studies conducted with different oral agents and their restenosis rates. The majority of these trials included a small number of patients and some failed to reproduce the same result in larger-scale trials. The reasons for failure of these trials include the following.

1. The long time-span from balloon angioplasty to the stent era. As we previously alluded to in section 2, the restenosis mechanisms are different between angioplasty and stenting.
2. Many of the trials involved a small number of patients, often <100. Therefore, the results were not reproducible in larger, multicentre trials such as the PRESTO trial.
3. The drug dosages required to achieve sufficient levels to inhibit restenosis are higher than therapeutic or tolerable dosages.
4. Bioavailability of the oral drugs depends on multiple factors, including drug metabolism and drug interactions.
5. Our understanding of the pathological mechanisms of restenosis is constantly evolving and the targets of therapy are changing.

4. Conclusion

In view of the limitations of drug-eluting stents, there is a definite role for systemic therapy for

Table III. Restenosis rates in various trials that showed positive results using oral agents

Trial	Oral agent	Number of patients	Restenosis (%)	
			drug	control
IMPRESS[10]	Prednisolone	83	7	33
REGRESS[11]	Pravastatin	221	7	29
TREAT-1[12]	Tranilast	255	17.6	39.4
TREAT-2[13]		297	25.9	41.9
ORAR[15]	Sirolimus	34	18.9	
ORBIT[45]		60	7.1 (2mg) 6.9 (5mg)	
Takagi et al.[16]	Troglitazone	52	NA	NA
Takagi et al.[17]	Pioglitazone	43	17	43
ESPRIT[18]	Cilostazol	117	5.4 (DCA + stent) 8.9 (DCA only)	
Kimishirado et al.[19]		130	13	31
CREST[20]		705	20.8	34.5
Swiss Heart Study[21]	Folic acid	553	9.9	16.0
MVT and Probucol Study Group[22]	Probucol	317	20.7	38.9
PART[23]		101	5.0	12.0
CART[24]		305	NA	NA
Ohsawa et al.[25]	Pemirolast	84	15	34.1
Fujita et al.[26]	Sarpogrelate	79	4.3	28.6
VAL-PREST[27]	Valsartan	250	19.2	38.6

CART = Canadian Antioxidant Restenosis Trial; **CREST** = Cilostazol for Restenosis Trial; **DCA** = directional coronary arthrectomy; **ESPRIT** = Elimination of restenosis after Stenting following Plaque Reduction with platelet Inhibitor Trial; **IMPRESS** = Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation Study; **MVT** = multivitamins; **NA** = not applicable; **ORAR** = Oral Rapamycin to prevent Restenosis – Argentina Single-Center Study; **ORBIT** = Oral Rapamycin to Inhibit Restenosis Trial; **PART** = Probucol Angioplasty Restenosis Trial; **REGRESS** = Regression Growth Evaluation Statin Study; **TREAT** = Tranilast Restenosis Following Angioplasty Trial; **VAL-PREST** = Valsartan for Prevention of Restenosis after Stenting.

restenosis. The focus of research involving oral agents for the treatment of restenosis is changing. While previous trials focused on antiplatelets, anticoagulants, lipid lowering and concomitant potential of anti-anginal agents such as calcium channel antagonists and β-adrenoceptor antagonists, newer trials are targeting inflammation, VSMC proliferation and inhibition of cell proliferation. Oral agents may potentially have a great impact on the practical application of restenosis therapy. The analogy of clopidogrel therapy compared with heparin-coated stents in preventing subacute thrombosis supports this contention. However, at the present time, we do not have the answer as to what would be the ideal agents of choice, the loading dose, maintenance dose and duration of therapy. On the basis of available experience with oral agents, we surmise that a high loading dose of an antiproliferative drug, followed by a tolerable maintenance dosage for a short duration, will suffice. Ongoing trials should answer this question within the next 2–3 years.

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Correspondence and offprints: Dr *Ron Waksman*, Washington Hospital Center, 110 Irving St, NW, Suite 4B-1, Washington, DC 20010, USA.
E-mail: ron.waksman@medstar.net