

Roles of Serotonin in Atherothrombosis and Related Diseases

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1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) was first identified as a powerful vasoconstrictor over a century ago (Rapport et al., 1948), and in the past 20 years has been recognized as an arterial smooth muscle mitogen (Nemecek et al., 1986). Serotonin is also known to act as a monoaminergic neurotransmitter in the brain and gastrointestinal tract, and is involved in a variety of functions, such as mood regulation, urine storage and voiding, the regulation of sleep and body temperature, food intake, and intestinal motility (Ni & Watts, 2006). Serotonin is predominantly synthesized and secreted into the blood stream by enterochromaffin cells in the gastrointestinal tract and is rapidly taken up and stored in small dense granules in platelets (Fanburg & Lee, 1997). In humans, 90% of the body's 5-HT is located in the intestines, and the rest is present primarily in platelets (8–9%) and the central nervous system (1–2%) (Fanburg & Lee, 1997). When platelets adhere and aggregate at sites of vessel injury, 5-HT is secreted and directly accelerates platelet aggregation (De Clerck, 1990; Wester et al., 1992).

The first step in the synthesis of 5-HT from tryptophan is the enzyme tryptophan hydroxylase (TPH), which is also the rate-limiting enzyme in its biosynthesis. TPH is known to have two isoforms, TPH-1 and TPH-2, which share an overall identity of approximately 70% (Walther et al., 2003). TPH-1 is mainly present in the pineal gland, thymus, spleen, and enterochromaffin cells of the gastrointestinal tract. TPH-2 is expressed solely in neuronal cells, such as the raphe nuclei of the brainstem. Finally, 5-HT is metabolized by monoamine oxidase A to form the metabolite 5-hydroxyindole acetic acid. Monoamine oxidase A is an intracellular enzyme and 5-HT must first be taken up into the cell prior to metabolism, and this achieved via the 5-HT transporter (Ni & Watts, 2006).

Serotonin is an extracellular mediator recognized by the 5-HT transporter and seven different receptors (5-HT₁–5-HT₇), giving rise to pleiotropic intracellular responses. All 5-HT receptors, with the exception of 5-HT₆, are involved in cardiovascular regulation. Central 5-HT_{1A}, 5-HT₃, and 5-HT₇ receptors play physiological roles in the regulation of cardiovascular reflexes, controlling changes in parasympathetic drive to the heart (Ramage

& Villalon, 2008). These reflexes also affect the activity of the sympathetic nervous system, which itself can be inhibited by stimulation of central 5-HT_{1A} receptors causing a drop in blood pressure and excited by 5-HT₂ receptor stimulation resulting in an increase in blood pressure. Acute vascular constriction by 5-HT is usually mediated by 5-HT_{1B} and 5-HT_{2A} receptors, except in the intracranial arteries in which constriction is mediated only through 5-HT_{1B} receptors (Kaumann & Levy, 2006). Both 5-HT_{1B} and 5-HT_{2A} receptors can mediate coronary artery spasm and pulmonary hypertension.

Serotonin promotes platelet aggregation and the proliferation, migration, and contraction of vascular smooth muscle cells (VSMCs). In addition to physiological hemostasis, these vascular responses play pivotal roles in the development and progression of atherothrombotic diseases.

2. Platelet aggregation

When platelets aggregate, 5-HT is released into the extracellular environment from the dense granules of activated platelets. The 5-HT thus released further activates other platelets by binding to 5-HT_{2A} receptors on the platelet membrane, contributing to thrombus formation (Satoh et al., 2006). Serotonin promotes further platelet recruitment and activates the coagulation pathway. The blood vessels in which platelets aggregate are exposed to high concentrations of 5-HT (Benedict et al., 1986).

3. Vasoconstriction

Serotonin is well known to act as a potent vasoconstrictor and has been shown to cause both vasoconstriction and vasodilation by interacting with receptors expressed on VSMCs, endothelial cells, or adrenergic nerve endings. In systemic arterial smooth muscle, 5-HT induces contractions only at sites of endothelial damage where platelet aggregation occurs, and this effect is antagonized by 5-HT₂ receptor antagonists (Sigal et al., 1991). Serotonin also amplifies the effects of other vasoconstrictors, such as histamine, angiotensin II, prostaglandin F_{2 α} , and noradrenaline (O'Rourke et al., 2006). The potent contractile effect of 5-HT may contribute to the vasoconstriction of coronary collateral vessels developed by reduction of coronary blood flow (Wright et al., 1992) and vasospastic disorders in arteries covered with regenerated endothelium and in atherosclerotic arteries (Sobey et al., 1991). The blood vessel wall chronically exposed to abnormally high blood pressure is characterized by increased vascular responsiveness to 5-HT. Chronic blockade of 5-HT_{2A} receptors reduces the development of hypertension in spontaneously hypertensive rats (Gradin et al., 1991).

4. VSMC proliferation

Serotonin stimulates the migration and proliferation of VSMCs through 5-HT_{2A} receptors (Tamura et al., 1997; Pakala et al., 1997, 1999a). Serotonin interacts synergistically with atherogenic lipoproteins (low-density lipoprotein [LDL] and β -very low density lipoprotein) (Koba et al., 1999, 2000), oxidized LDL and its major components, such as lysophosphatidylcholine, 4-hydroxy-2-nonenal, and reactive oxygen species (Watanabe et al., 2001a, 2001b) in inducing VSMC proliferation. Serotonin also potentiates the mitogenic

effects of other vasoactive agents, such as endothelin-1, angiotensin II, urotensin II, and thromboxane A₂ (Watanabe et al., 2001c, 2001d, 2001e; Pakala et al. 1997), platelet-derived microparticles (Pakala, 2004), coagulation factors, such as thrombin and coagulation factor Xa (Pakala & Benedict, 1999; Pakala, 2003), and monocyte chemoattractant protein-1 on VSMCs (Watanabe et al., 2001f). In addition, 5-HT stimulates the expression of interleukin-6 and cyclooxygenase-2 in VSMCs (Ito et al., 2000; Machida et al., 2011).

5. Endothelial cell function

Serotonin stimulates the expression of tissue factor and plasminogen activator inhibitor-1 in endothelial cells through 5-HT_{2A} receptors (Kawano et al., 2001). Serotonin-stimulated endothelial cells secrete a T lymphocyte-specific chemotactic cytokine with competence growth factor activity (Katz et al., 1994). Serotonin, alone and combined with thromboxane A₂, potently induces endothelial cell proliferation (Pakala et al., 1994, 1999b). However, there is still controversy regarding the effects of 5-HT on endothelial cell proliferation (Ruiz-Perez et al., 2011).

6. Macrophage foam cell formation

Serotonin stimulates monocyte adhesion (Lorenowicz et al., 2006), and enhances macrophage foam cell formation associated with increased uptake of oxidized LDL (Aviram et al., 1992) and up-regulation of acyl-coenzyme A:cholesterol acyltransferase-1 (ACAT-1) through 5-HT_{2A} receptors (Suguro et al., 2006).

7. 5-HT_{2A} receptor blockade

The roles of 5-HT in the pathogenesis of atherothrombotic diseases are revealed by the results of pharmacological interventions involving 5-HT_{2A} receptors. Functional analyses of the roles of 5-HT in the cardiovascular system using 5-HT_{2A} receptor knockout mice have not been performed. Several studies performed before the discovery of specific and/or selective 5-HT_{2A} receptor antagonists indicated that 5-HT₂ receptor blockers inhibit angioplasty-induced vasospasm and microvascular constriction following atherosclerotic plaque rupture in atherosclerotic rabbit models (Sigal et al., 1991; Taylor et al., 2004).

Sarpogrelate, a selective 5-HT_{2A} receptor antagonist, inhibits responses to 5-HT mediated by 5-HT_{2A} receptors, such as platelet aggregation and thrombus formation (H Hara et al., 1991a; Nishihira et al., 2006), and prevents the development of atherosclerotic lesions (H Hara et al., 1991b; Hayashi et al., 2003), vasospasm (Miyata et al., 2000), and intimal hyperplasia in vein grafts after bypass grafting (Kodama et al., 2009). This drug suppresses ACAT-1 expression in macrophages (Suguro et al., 2006), vascular oxidative stress and VSMC proliferation (Watanabae et al., 2001d; Sun et al., 2011), up-regulates endothelial nitric oxide synthase (Hayashi et al., 2003), and reduces the expression of matrix metalloproteinase-1 that degrades the arterial extracellular matrix (Hayashi et al., 2003), contributing to stabilization of vulnerable plaque.

8. 5-HT concentration and Cardiovascular Disease

In a previous study involving the measurement of washed platelet-bound 5-HT concentration in three groups based on the presence and absence of thrombotic diseases,

platelet 5-HT levels were highest in patients with deep-vein thrombosis and pulmonary embolism prior to death from thrombotic events. The lowest levels were detected in subjects without thrombosis, and intermediate levels were seen in patients with cerebral thrombosis (Misra et al., 1975). These findings suggested that 5-HT plays an important role in the initiation of thrombus formation.

With regard to the association between 5-HT and coronary artery disease (CAD), it has been reported that coronary sinus plasma samples from CAD patients evoked vasoconstriction, whereas systemic artery and venous samples from patients without CAD did not (Rubanyi et al., 1987). In addition, the vasoactive activity of the coronary sinus plasma showed a positive correlation with the severity and extent of coronary artery narrowing, and among various pharmacological interventions only methiothepin, a non-selective 5-HT receptor antagonist, prevented the vasoconstriction induced by these coronary sinus plasma samples. Although this study did not measure 5-HT concentration directly, these results suggested that the amount of 5-HT released into the coronary sinus plays an important role in vasoconstriction in the coronary circulation. The first direct measurement of 5-HT concentration in human coronary circulation was reported by van den Berg and co-workers (van den Berg et al., 1989), who measured 5-HT concentration by modified radioenzymatic assay (Benedict et al., 1986; Hussain & Sole, 1981) in platelet-poor plasma obtained from the central aorta and coronary sinus of 52 patients referred for cardiac catheterization. The 5-HT concentration in the coronary circulation determined by subtracting the levels in the aorta from those in the coronary sinus is significantly higher in patients with CAD compared with those without CAD (0.6 ± 6.6 ng/ml vs. -5.6 ± 10.3 ng/ml, mean \pm SD, $p < 0.05$). These concentrations were significantly higher in CAD patients with complex coronary lesions compared with those with smooth concentric lesions (3.1 ± 5.5 ng/ml vs. -1.9 ± 6.6 ng/ml, $p < 0.02$). A similar method was used to measure 5-HT concentration in coronary circulation in 8 patients with CAD undergoing plain old balloon angioplasty (POBA) (Golino et al., 1994). The 5-HT levels in the coronary sinus increased significantly after POBA, while those in the aorta did not change. Coronary constriction distal to the site of dilation observed after POBA was positively correlated with the 5-HT concentration in the coronary circulation, and this coronary constriction was inhibited by pretreatment with the 5-HT_{2A} receptor antagonist, ketanserin. Other studies using similar techniques have shown that the transcardiac 5-HT concentration is significantly higher in patients with variant angina pectoris compared with non-CAD controls (Murakami et al., 1996, 1998). These studies demonstrated that 5-HT released from activated platelets plays an important role in the pathogenesis of CAD in humans. However, the methods used in these studies required invasive procedures.

Vikenes and co-workers measured 5-HT concentrations in platelet rich plasma from venous blood using high-performance liquid chromatography (HPLC) in 122 men undergoing coronary angiography (Vikenes et al., 1999). Their data indicated that total 5-HT concentration was positively correlated with platelet count ($r = 0.552$, $p < 0.001$), and both total 5-HT concentration and platelet counts were significantly higher in patients with CAD compared with those without CAD. The difference in 5-HT level was greatest in men aged ≤ 60 years old, and the difference reduced steadily with age. The high 5-HT concentration ≥ 1 $\mu\text{mol/l}$ was significantly associated with CAD, with an odds ratio (OR) of 3.84 (95% confidence interval [CI] 1.12–13.11), independently of age and smoking. During a mean follow-up period of 44 ± 15 months, Kaplan-Meier cardiac event-free survival curves for

CAD patients aged ≤ 70 years old indicated a better prognosis with regard to cardiac events for patients with low 5-HT ($< 1 \mu\text{mol/l}$) (log rank test, $p < 0.05$). Venous plasma 5-HT concentration measured by radioimmunoassay was reported to be significantly higher in patients with variant angina pectoris than in those with healed myocardial infarction or controls (Figueras et al., 2005). On the other hand, comparison of 5-HT concentration in platelet-poor plasma and whole blood indicated that plasma 5-HT concentration tended to increase with age, while its concentration in whole blood decreased (K Hara et al., 2004). The ratio of plasma to whole-blood concentration of 5-HT was significantly higher in various types of CAD, such as variant angina pectoris, acute coronary syndrome (ACS), and prior myocardial infarction, compared with healthy controls, whereas whole-blood 5-HT levels were somewhat higher in healthy controls than in patients with effort angina. The ratio of plasma to whole-blood concentration of 5-HT was recently demonstrated to be positively correlated with Framingham 10-year risk scores for CAD (Y Hirowatari et al., 2011). These clinical studies suggested that high levels of 5-HT are significantly associated with atherosclerotic cardiovascular diseases and the occurrence of cardiovascular events. Thus, 5-HT plays a key role in the pathogenesis of atherothrombosis.

9. 5-HT_{2A} receptor blocker and treatment of CAD

Several clinical studies with 5-HT_{2A} receptor blockers have supported the experimental results demonstrating that 5-HT plays an important role in the development of CAD due to platelet aggregation, VSMC constriction, and migration and proliferation of VSMCs. In a study of 22 patients with stable effort angina, oral administration of 200 mg of sarpogrelate 1 hour prior to treadmill exercise test was shown to improve exercise capacity and the severity score determined by myocardial perfusion scintigraphy in 12 patients with well-developed collateral flow evaluated by coronary angiography, whereas sarpogrelate affected neither exercise time nor severity score in other patients without collateral flow (Tanaka et al., 1998). This was confirmed in another study involving 2 weeks of treatment with 300 mg of sarpogrelate in 20 patients with stable angina pectoris (Kinugawa et al., 2002); treatment with sarpogrelate significantly increased the specific activity scale score, increased exercise time and rate-pressure product, an index of myocardial oxygen consumption, at onset of ischemic ST depression ≥ 0.1 mV on electrocardiogram, and decreased the number of anginal attacks only in patients with angiographically proven well-developed collateral flow. On the other hand, sarpogrelate showed no effects in the patients without well-developed collateral flow. Similar results were obtained in another study with intravenous injection of another 5-HT_{2A} receptor antagonist, ketanserin (Kyriakides et al., 1999). In a study of stable angina pectoris patients with single-vessel disease, ketanserin increased coronary collateral blood flow and decreased myocardial ischemia during POBA. In a study of 15 CAD patients without significant stenosis ($< 75\%$ diameter stenosis) in the left anterior descending coronary artery, oral administration of 200 mg of sarpogrelate increased the coronary blood flow velocity at both baseline and hyperemia evaluated by intracoronary Doppler guidewire without any effects on systemic blood pressure or cardiac output (Satomura et al., 2002). On the other hand, there were no significant differences in baseline or hyperemic coronary blood flow velocity in the control group. These results suggested that sarpogrelate augments coronary flow reserve by inhibiting 5-HT-induced coronary vasoconstriction and platelet aggregation in collateral vessels in CAD patients.

In a comparative study of the effects of oral administration of sarpgrelate administration (200 mg) or placebo in addition to aspirin and ticlopidine 60 minutes before POBA in 20 patients with stable effort angina with a de novo single stenotic lesion of 75%–90%, length < 20 mm in the proximal left anterior descending coronary artery, sarpgrelate significantly reduced the ischemic ST changes after coronary angioplasty compared with the placebo group with no changes in collateral blood flow, blood pressure, or heart rate (Horibe et al., 2004). These observations suggested that sarpgrelate improves myocardial ischemic injury by pharmacological ischemic preconditioning rather than by stimulating collateral development.

Studies investigating the effects of 5-HT_{2A} receptor blockers on prevention of restenosis after coronary angioplasty yielded conflicting results between ketanserin and sarpgrelate. In a small placebo-controlled study, 24-hour infusion of ketanserin following POBA prevented the early restenosis evaluated at 24 hours after POBA but failed to prevent restenosis at 4 to 9 months after POBA (Klein et al., 1990). The Post-Angioplasty Restenosis Ketanserin (PARK) study was a randomized, double-blind, placebo-controlled trial to assess the effects of ketanserin in prevention of restenosis after POBA (Serruys et al., 1993). A total of 658 patients with stable or unstable angina pectoris who were scheduled to undergo elective POBA received either ketanserin (loading dose, 40 mg 1 hour before POBA; maintenance dose, 40 mg bid for 6 months) or placebo. All patients received aspirin for 6 months. The primary clinical end points were defined as any one of the following: cardiac death, myocardial infarction, or the need for repeat angioplasty or bypass surgery of the previously dilated sites between the first POBA and 6 months after POBA. The relative risk of the primary end points for the ketanserin group compared with the placebo group was 0.89 (95% CI 0.70–1.13). The restenosis rate according to > 50% stenosis and the quantitative angiographic findings were similar between the two groups. The PARK study failed to show that ketanserin could prevent restenosis and improve clinical outcome after POBA. On the other hand, in an investigation of the effects of sarpgrelate in prevention of restenosis after coronary stenting in Japanese patients with stable angina pectoris, pretreatment with sarpgrelate for 3 days before coronary stenting and continuation of 300 mg of sarpgrelate for 6 months in addition to 81 mg of aspirin and 200 mg of ticlopidine markedly reduced restenosis rate at 6 months after coronary stenting compared with the non-sarpgrelate treatment group (4.3% vs. 28.6%, $p < 0.005$) (Fujita et al., 2003). The results of multivariate logistic regression analysis showed that treatment with sarpgrelate was a significant predictor for angiographic restenosis, independent of the findings of quantitative coronary angiography, stent characteristics, and the presence of diabetes. These two studies differed in 5-HT_{2A} receptor blocker drug characteristics and pretreatment period as well as the angioplasty procedure. The latter study supported the suggestion that sarpgrelate may prevent the development of intimal hyperplasia due to VSMC proliferation. Further randomized controlled trials to investigate the effects of sarpgrelate on prevention of restenosis after placement of drug-eluting stents are required.

10. 5-HT_{2A} receptor blocker and treatment of Peripheral Artery Disease

Sarpgrelate is widely used clinically as an anti-platelet drug for prevention of thrombosis and treatment of critical limb ischemic symptoms in patients with peripheral artery disease (PAD), such as arteriosclerosis obliterans (ASO) and Buerger's disease. In a study by

Miyazaki and colleagues (Miyazaki et al., 2007), 22 patients with PAD received either sarpogrelate at a dose of 300 mg orally or conventional therapy for 12 weeks. Both forearm and leg endothelium-dependent vasodilation were improved and maintained for 24 weeks in patients treated with sarpogrelate whereas no improvement was observed in patients treated with conventional therapy. In addition, endothelium-nondependent vasodilation was similar between the two treatment groups. These results suggest that 12 weeks of treatment with sarpogrelate improved vascular endothelial function in PAD patients. Further they investigated the effects of a combination of bone marrow mononuclear cell implantation and sarpogrelate on endothelial function in 16 PAD patients (Higashi et al., 2010). They performed the evaluations before and after bone marrow mononuclear cell implantation in 16 patients with critical limb ischemia. A 12-week course of sarpogrelate treatment amplified the increased leg blood flow responses to acetylcholine evaluated by plethysmography induced by bone marrow mononuclear cell implantation compared with conventional treatment, whereas bone marrow mononuclear cell implantation improved limb ischemic symptoms in the sarpogrelate group as well as in the conventional treatment group. These two studies showed that a treatment with sarpogrelate for at least 12 weeks has a beneficial effect on vascular endothelial function in PAD patients treated with conventional therapy.

There have been several small studies of the effects of sarpogrelate on various biomarkers without controls in PAD patients. In a study of 13 patients with ASO, treatment with sarpogrelate for 1 week decreased adenosine diphosphate (ADP)- or collagen-induced platelet aggregation and reduced the releases of platelet-derived growth factor, soluble P-selectin, and transforming growth factor- β 1 from platelets stimulated by ADP or collagen (Nakamura et al., 2001). In a study of 24 non-diabetic and non-medicated diabetic patients with PAD (Fontaine grades 1 and 2), 300 mg of sarpogrelate decreased insulin resistance at 2 weeks and 3 months after treatment, and increased plasma levels of adiponectin at 3 months after treatment (Kokubu, 2006). Similarly, 300 mg of sarpogrelate increased adiponectin levels at 2 and 3 months after treatment in 8 diabetic patients with ASO (Yamakawa et al., 2003). Treatment with 300 mg of sarpogrelate improved limb ischemic symptoms and decreased interleukin-18 levels in 8 diabetic patients with ASO (Yamakawa et al., 2004). In a study of 10 patients with Buerger's disease, 8 weeks of treatment with 300 mg of sarpogrelate was well-tolerated. However, platelet aggregation induced by 5-HT increased significantly after 2 and 4 weeks, and whole-blood 5-HT concentration increased significantly after 2 weeks of treatment (Rydzewski et al, 1996).

11. 5-HT_{2A} receptor blocker and treatment of ischemic cerebrovascular disease

There have been no reports of high plasma 5-HT levels in patients with stroke at the acute phase. In a study of elderly subjects, plasma 5-HT concentration measured by enzyme immunoassay was significantly higher in patients with vascular dementia caused by stroke or atherosclerotic small vessel disease compared with age-matched controls (Ban et al., 2007).

In a double-blind, controlled, clinical-pharmacological study, 47 patients with ischemic stroke who discontinued any antiplatelet agents and anticoagulants or fibrinolytic agents,

were randomly assigned to receive one of three daily doses of sarpogrelate, i.e., 75, 225, or 300 mg, for 7 days (Uchiyama et al., 2007). Sarpogrelate treatment inhibited platelet aggregation induced by 5-HT plus adrenaline in a dose-dependent manner. The Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS) trial was a randomized, double-blind, controlled trial to evaluate and compare the efficacy and safety of sarpogrelate with those of aspirin for prevention of recurrence in patients with ischemic stroke (Shinohara et al., 2008). A total of 1050 patients with recent ischemic stroke (1 week to 6 months after onset) were randomly allocated to receive either 300 mg of sarpogrelate or 81 mg of aspirin with a mean duration of follow-up of 1.59 years (maximum: 3.37 years). The annual recurrence rates of cerebral infarction were 6.09% (95% CI 4.83–7.67) with sarpogrelate and 4.86% (3.75–6.28) with aspirin. The hazard ratio (HR) was 1.25 (95% CI 0.89–1.77); the upper limit of 95% CI of the HR exceeded 1.33, indicating that sarpogrelate was slightly inferior to aspirin in preventing the recurrence of cerebral infarction. On the other hand, the incidence rates of serious vascular events, defined as stroke, ACS, or vascular event-related death, were similar between the sarpogrelate and aspirin group. There were significantly fewer bleeding events in the sarpogrelate group compared with the aspirin group (11.9%, 95% CI 9.6–14.4 vs. 17.3%, 14.7–20.2, respectively, $p < 0.005$). In subgroup analysis in the S-ACCESS trial, sarpogrelate was shown to be inferior to aspirin in most subgroups except diabetic patients (Shinohara & Nishimaru, 2009). Thus, sarpogrelate may be a useful treatment option for Japanese stroke patients with diabetes.

12. Conclusion

This review presented a discussion of the potential involvement of 5-HT mediated through 5-HT_{2A} receptors in the development of atherothrombotic cardiovascular diseases, including platelet aggregation, thrombus formation, VSMC contraction, and arterial intimal hyperplasia. These responses are synergistically augmented with other vasoactive compounds, atherogenic lipids, and various inflammatory cytokines. The 5-HT_{2A} receptor antagonists inhibit the 5-HT-mediated atherothrombotic process. Although ketanserin inhibits not only 5-HT_{2A} receptors but also α 1-adrenergic and histamine H₁ receptors, it was withdrawn due to its tendency to induce proarrhythmia. Sarpogrelate is a specific 5-HT_{2A} receptor antagonist that has been reported to have various beneficial effects especially in patients with CAD and/or atherosclerotic cardiovascular disease with diabetes, and to have fewer adverse effects compared with other anti-platelet agents. However, larger randomized controlled trials of sarpogrelate in CAD, PAD, stroke, and diabetes are required.

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14. References

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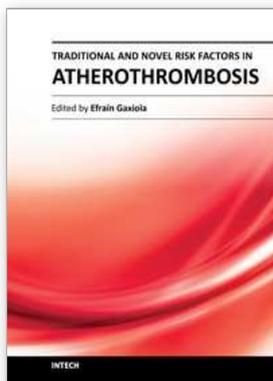
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Traditional and Novel Risk Factors in Atherothrombosis

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Atherothrombosis has reached pandemic proportions worldwide. It is the underlying condition that results in events leading to myocardial infarction, ischemic stroke and vascular death. As such, it is the leading cause of death worldwide manifested mainly as cardiovascular/cerebrovascular death. The complex and intimate relationship between atherothrombosis and traditional and novel risk factors is discussed in the following chapters of Traditional and Novel Risk Factors in Atherothrombosis - from basic science to clinical and therapeutic concerns. Beginning with pathology and pathophysiology of atherothrombosis, plaque rupture/disruption, this book continues with molecular, biochemical, inflammatory, cellular aspects and finally analyzes several aspects of clinical pharmacology.

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