GENES and In-Stent Restenosis: Review

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ABSTRACT

The initiation of coronary stents is a vast landmark in the practice of interventional cardiology. The vascular injury sustained during the percutaneous coronary intervention (PCI) leads to a complicated inflammatory and repairing process. Therefore, stent restenosis arises. Diabetes mellitus is the highest-risk clinical predictor of ISR. Genetics has an important role in the development of ISR. There is a suggested association between the appearance of stent restenosis and certain genetic polymorphisms. Examples of these single nucleotide polymorphisms are endothelial nitric oxide synthase gene (eNOS), the angiotensin converting enzyme gene (ACE), the angiotensin II type 1 receptor gene (AT1R), TGF-β, and VEGF. CYP2C19 variants can help change the medical strategy to a more individualized therapeutic regimen either by altering the therapeutic dose depending on the genotype or using an alternative drug that does not worsen the patient's case. However, eNOS polymorphism produces gene expression alteration leading to ISR following stent placement. In addition, the deletion-allele of the ACE genotype increases the risk of ISR; however, the I allele decreases the risk. Moreover, the D/I polymorphism is not an independent factor of ISR in patients administering ACE inhibitors or angiotensin receptor antagonists. Furthermore, studies on large sample sizes are required to decrease the harmful adverse effects of stent restenosis by detecting these allele gene polymorphisms.

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INTRODUCTION

The initiation of coronary stents is considered as an immense turning landmark in the application of cardiology. A lot of obstacles faced the conventional percutaneous transluminal coronary angioplasty (PTCA). Some of these were mechanical complications like coronary dissection and abrupt vessel closure. The others were the high incidence of restenosis around 40–50% of cases. Despite these obstacles, coronary stents continue to develop procedural profit with significantly diminishing restenosis following coronary intervention. Accordingly, the placement of a bare metal stent (BMS) was the most common coronary intervention (Brophy *et al.*, 2003).

Restenosis within BMS was considerable in the range of 20 to 40% despite the advances in stent procedural techniques and pharmacological strategies. Thus drug-eluting stents (DES) were emerged to reduce the incidence of ISR despite the absolute ascertained reduction, which relied mainly on when

and how to use it properly (Kastrati *et al.*, 2006).

The goal of this review is to introduce a comprehensive overview of both BMS and DES restenosis, focusing on contemporary and investigational treatment modalities and their relationship with genes, especially Cyt 2C19*2, Cyt 2C19*3, eNOS, and ACE.

The vascular injury sustained during the percutaneous coronary intervention (PCI) leads to a complicated inflammatory and repairing process. Therefore, stent restenosis arises. Restenosis involves two mechanisms: Firstly, vascular elastic recoil and thrombus formation, which usually takes place after coronary surgery. Secondly, a repairing process, which includes complicated coagulation and inflammatory factors, stimulates the formation of extracellular matrix and proliferation of smooth muscle cells, and this process is known by neointimal hyperplasia. Both first and second mechanisms stimulate the ISR to occur (Schwartz and Henry, 2019). After three months, the most extreme restenosis of the curable segment is observed, and it continues almost the same after six months. On the other hand, DES provides maintained liberation of implanted anti-inflammatory and anti-proliferative agents with a subsequent reduction in neointimal growth and retardation of the vessel's repairing process by years (Schwartz and Henry, 2019).

CAUSES OF STENT RESTENOSIS

Generally, predicting factors for ISR are categorized into three fundamental classes: patient, vessel, and procedural predictors. Minimizing these risky components by significant adjustment of these components, especially for patient and vessel factors or by accurate expert assessment for procedural factors, results in significant inhibition of restenosis incidence after stent placement. Diabetes mellitus constitutes the highest-risk clinical predictor of ISR compared to the other patient-related predictors, the risk of restenosis following BMS implantation by 30–50% (Mathew *et al.*, 2004). This is almost the same incidence of restenosis in diabetic patients compared to non-diabetic after PCI with DES. However, practicing DES, when compared to BMS, has cut down the rate of ISR in diabetic patients (Mathew *et al.*, 2004) .There are a lot of factors that increase the incidence of ISR in diabetic patients. Some of them are systemic as the variance of inflammatory agents exists, and others are anatomic as narrow diameters of vessels and extended lesions surely magnify the incidence of ISR. Therefore, wider diameters and shorter lesions significantly decrease the incidence of restenosis (Lemos *et al.*, 2004a) . Mostly, despite the existence or absence of dia-

betes, the rate of angiographic restenosis is significant with the association between lesion length and diameter. There are several procedural factors for ISR that should be considered. One of them can be illustrated by clinical reports, which show that 2nd generation stents integrating thinner struts have a significant decrease in restenosis and less need for revascularization than 1st gen stents integrating thicker struts. (Yoshitomi *et al.*, 2001). New evolving stent designs target to produce platforms with thinner stent strut filaments. In addition, the length of the stent is a powerful independent factor for ISR, which almost duplicate the risk for ISR, especially when the length is less than 0.2 cm compared to when the length is more than 0.35 cm (Kobayashi *et al.*, 1999) . Eventually, the cornerstone in anticipating the rate of ISR is the minimal luminal diameter(MLD).

STENT RESTENOSIS THERAPY

ISR is considered as a critical issue in either BMS or DES. Some patients with acute coronary syndrome and ST elevation myocardial infarction is associated with significant ISR (Kasaoka *et al.*, 1998). For these patients, the best medical care for their alleviation is repeat revascularization. Although coronary stent positioning after PTCA is commonly implanted to overcome restenosis, the most effective revascularization option (either BMS or DES) in patients developing ISR is controversial. Different approaches for treating ISR that range from PTCA to vascular brachytherapy (VBT) have been examined extensively; however, unsatisfactory outcomes were obtained with recurrent rates of restenosis ranging from 20–40% (Kasaoka *et al.*, 1998). The challenge now is dealing ideally with the restenosis raised after DES implantation. However, there are hopeful results from DES implantation to overcome restenosis after BMS implantation.

Previously, the repetition of PTCA was the mainstay treatment for ISR. The incidence of restenosis remained undesirably elevated by about 40% with more elevated incidence after diffuse ISR therapy despite the promising outcomes of balloon angioplasty (Kini *et al.*, 2000).

Previous studies explained the high rate of recurrent restenosis following PTCA based on the significantly smaller dimension of lumen following PTCA when consistently compared with the following stent implantation (Kini *et al.*, 2000) . The effectiveness of PTCA may be restricted by the stenosis after PTCA and the fundamental modifications to arterial walls around the stent, which results in diminishing in MLD and inducing higher restenosis

incidence.

There are fluctuating results about the conjugation of PTCA with plaque repairing therapies e.g., rotational atherectomy and coronary laser angioplasty. These are performed to cut down the recurrence of restenosis after ISR therapy (Sharma *et al.*, 1998) . Unexpectedly, some studies investigating debulking strategies center on clinical restenosis e.g., target vessel revascularization [TVR] or target lesion revascularization [TLR] instead of angiographical restenosis. Additionally, various studies assure that PTCA and rotational atherectomy in comparison with PTCA alone decreased the incidence of clinical consequences after one year of angioplasty (Sharma *et al.*, 1998) . The trials of rotational atherectomy for overcoming ISR were similar to those of excimer laser angioplasty regarding the one-year TLR incidence (Sharma *et al.*, 1998). Vascular brachytherapy was the single treatment for ISR before the appearance of DES. Vascular brachytherapy necessitates a radiation source that emits β or γ rays through a catheter around the area of restenosis for a few minutes. Various studies indicated that vascular brachytherapy significantly diminishes restenosis and decreases the need for repeat revascularization after 12 months of observation (Malhotra and Teirstein, 2000).

Mostly, various studies comparing DES implantation versus Rotational atherectomy, vascular atherectomy, balloon angioplasty, and CABG surgery indicated the complete advantage of DES, which significantly reduces clinical consequences and angiographic restenosis (Lemos *et al.*, 2004b).

GENES & STENT RESTENOSIS

Either stable coronary artery disease (CAD) or acute coronary syndrome has a complicated confronting complication after implantation of coronary stent known as In-stent restenosis (ISR). The stent generation has driven invasive cardiology forward to the modern generation of operations' disadvantages, including ISR (Kim and Dean, 2011) . Genetics - as ACE gene or eNOS gene - may perform a crucial province in the improvement of ISR between CAD patients. Endothelin-1, TGF-β, VEGF, angiotensin II, and nitric oxide (NO) are set free from damaged endothelial cells participating in the hyperplasia of endomembrane and cell proliferation of smooth muscle leading to a subsequent increase in ISR (Schwartz and Henry, 2019) .

Several studies inspected the consequences of polymorphisms on ISR in genes, especially encoding various receptors, enzymes, and growth factors. Although several reports have not indicated the implied purposes of functional polymorphisms in several genes such as endothelial nitric oxide synthase gene (eNOS), angiotensin converting enzyme gene (ACE), angiotensin II type 1 receptor gene (AT1R), TGF-β, and VEGF, these studies indicated an association between ISR and single nucleotide polymorphisms (SNPs) in these genes (Gomma, 2002; Osadnik *et al.*, 2016).

Genetic alteration resulting in variation in one specific location leading to a substantial alteration in coded protein is known as single nucleotide polymorphism (SNP), which causes more than 90% of the genetic changes in humans and this may depend on various factors (Mccarroll *et al.*, 2008). An important clinical obstacle that should be considered is the alteration of individuals' responses to drugs, which may rely on different factors like body weight, gender, genetics, age, organ function, drug interactions, disease states, culture, lifestyle, smoking, and diet (Brockmöller and Tzvetkov, 2008). From these different factors, genetic alteration has a superior percentage of up to 95%, which can change individuals' responses to drugs (Brockmöller and Tzvetkov, 2008).

We may understand why the repetition of stent implantation is still required and whether these patients may be determined and assisted with genetic screening if we can relate ISR and SNPs.

CAD is provided by many factors; however, a few of them affect ISR. Therefore, it will be promising to screen stable CAD cases for SNPs causing ISR, then take appropriate precautions to diminish these complications. One example of that is the several studies showing that SNPs of genes coding angiotensin converting enzyme (rs1799752) may cause CAD; however, it fails to confirm ISR.

CYTOCHROME 2C19 GENE

Clopidogrel is a prodrug that necessitates hepatic biotransformation to compose an active metabolite that diminishes P2Y12, the adenosine diphosphate (ADP) receptor (Sibbing *et al.*, 2008), therefore decreases platelet aggregation. Accordingly, it is applied in atherothrombotic consequences after percutaneous coronary intervention (PCI) with stent implantation (Cuisset *et al.*, 2006). Awkwardly, only a few percent (about 15%) is transformed into an active form, and the rest is disintegrated into inactive forms. Transformation of clopidogrel to its active metabolite requests two consecutive oxidative processes, which include various CYP450 enzymes such as CYP3A4, CYP1A2, CYP2B6, CYP2C9, and CYP2C19 (Bouman *et al.*, 2011). CYP2C19 gene as a part of the CYP450 class

is responsible for the metabolism of various drugs as antidepressants, benzodiazepines, some proton pump inhibitors, and clopidogrel.

Common CYP2C19*2 (rs4244285) is the most frequent loss of function allele with an incidence of up to 15% in Caucasians and Africans and around 30% in Asians (Harmsze *et al.*, 2010). On the other hand, CYP2C19*3–*8 possesses less or no enzymatic activity; however, their incidence is less than 1% except for CYP2C19*3 (rs4986893) which is up to 9% (Hulot, 2006). According to CYP2C19 genotypes, subjects may be classified as powerful metabolizers (as *1/*1), moderate metabolizers (as *1/*2), or weak metabolizers (as *2/*2). The incidences of CYP2C19 weak metabolizers are up to five percent in Africans and Caucasians and up to seventeen percent in Asians. On the other hand, the CYP2C19*17 allele (rs12248560) causes elevated activity and those with (*17/*17) may be classified as ultrarapid metabolizers as some studies show that individuals with this allele have enhanced platelet inhibition and more clopidogrel response, and perhaps a raised bleeding drawback (Frére *et al.*, 2009) .

One study confirmed that the CYP2C19*2 allele was related to an exaggerated frequency of stent thrombosis in about 12 months following stent implantation (Oh *et al.*, 2012).

Eventually, it is essential to consider the different characteristics of CYP2C19 variants that may assist in changing the present medical strategy to a more individualized therapeutic regimen that proposes two options: first is the alteration of therapeutic dose depending on the genotype and second is the use of an alternative drug that does not deteriorate the patient case (Lee, 2013).

ENOS GENE

Endothelial dysfunction is represented by the deterioration of endothelium as a result of the reduction of the production of nitric oxide (NO) in the vessel which is considered as a risk element in the development of ISR as it has biological impacts as vasodilation, smooth muscle cell growth reduction, antiatherosclerotic properties, antiplatelet characteristics, and diminishing the attachment of white cells to the blood vessel surface (Liu and Huang, 2008).

One study confirmed that 786C allele reduces the transcriptional action of eNOS (Liu and Huang, 2008). Furthermore, this former study confirmed that cases with eNOS T786C mutation have lower nitrate concentrations than others without this mutation (Liu and Huang, 2008). Accordingly, diminished NO synthesis causes SMC proliferation

and neointimal hyperplasia resulting in ISR.

Various reports showed a direct association between eNOS T786C mutant allele existence and the appearance of cardiovascular disease in Asian subjects. An extensive report indicated a positive correlation between eNOS T786C polymorphism and the existence of coronary heart disease in variant populations (Rai *et al.*, 2014).

It is a unique area of concern to relate between the T786C polymorphism and ISR after PCI with BMS implantation in CAD. It was confirmed that T786C and G298A polymorphisms influenced the result following BMS implantation, in which the C allele of the T786C polymorphism was a risk factor for ISR (Gomma, 2002).

From the eN0S polymorphisms, G298A has been broadly examined for a promising relationship with cardiovascular disease. Gomma et al. indicated that A allele of the G298A polymorphism is a strong predictor for ISR (Gomma, 2002).

Furthermore, individuals with 298 Asp allele of the eNOS (rs1799983) polymorphism demonstrated a higher incidence of ISR than 298Glu homozygotes (Gomma, 2002).

In conclusion, eNOS polymorphism causes gene expression alteration leading to ISR following stent implantation.

ACE GENE

Smooth muscle cell proliferation is activated by angiotensin converting enzyme (ACE). Additionally, deletion/insertion (D/I) polymorphism of the ACE gene regulates ACE plasma levels (Rigat *et al.*, 1990).

Interestingly, one study performed by Jørgensen et al. shows that the Deletion-allele of the ACE genotype was related to increased late lumen loss, therefore higher incidence of ISR and suggesting that Deletion-allele is a risk factor for ISR. Additionally, this study also demonstrates that insertion-allele decreases the incidence of ISR (Jørgensen *et al.*, 2001).

The D/I polymorphism has not been considered as a risk factor of ISR. Still, it might have a practical impact in cases having ACE inhibitors or angiotensin receptor antagonists in their therapeutic (Jørgensen *et al.*, 2001).

OTHER GENES

A study performed by Osadnik et al. demonstrated that TGF-β1 polymorphisms (rs1800470, rs2285094, and rs6999447) following the modification of various risk factors had a positive correlation

with ISR following DES implantation (Osadnik *et al.*, 2016). VEGF potentially stimulates endothelial cell migration and therefore regulates vascular healing. Moreover, a VEGF polymorphism was associated with restenosis after BMS implantation (Osadnik *et al.*, 2016).

CONCLUSIONS

Genetics - as ACE or eN0S gene - perform a crucial function in the occurrence of ISR between CAD patients. There is an association between the development of ISR or CAD and genetic polymorphism. A personalized therapeutic regimen of individuals with these genetic alleles may enhance the clinical consequences. Furthermore, studies on large sample sizes are required to decrease the harmful adverse effects of stent restenosis by detecting these allele gene polymorphisms.

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Conflict of Interest

No conflict of interest was declared.

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