Diabetic dyslipidemia in type 2 diabetes (T2DM) is characterized by elevated levels of triglycerides (TG), decreased levels of high density lipoprotein-cholesterol (HDL-C), elevated levels of low density lipoprotein-cholesterol (LDL-C), and the predominance of small and dense LDL particles (sdLDL). The mechanism underlying diabetic dyslipidemia remains unclear. Insulin resistance is believed to be an important determinant. Mechanisms underlying insulin resistance-induced diabetic dyslipidemia seem to be related to apolipoprotein CIII (ApoCIII), a known inhibitor of lipoprotein lipase. The concentration of very low density lipoprotein (VLDL) with a higher TG content and abundant ApoCIII was found to be significantly elevated in patients with T2DM. Recently, volanesorsen as a promising Apolll inhibitor was shown to improve the lipid profile in patients with diabetic dyslipidemia. Herein, this paper will review recent advance in pathophysiology of diabetic dyslipidemia and the role of ApoCIII in this condition, with focus on describing a novel drug volanesorsen as potential treatment strategy.

Keywords
Apolipoprotein CIII; type 2 diabetes mellitus; diabetic dyslipidemia; high density lipoprotein-cholesterol; low density lipoprotein-cholesterol; very low density lipoprotein; volanesorsen

1. Introduction
Dyslipidemia may be classified as primary or secondary. Primary dyslipidemia results from genetic defects that directly affect the metabolism of lipoproteins, whereas secondary dyslipidemia results from other disorders that indirectly affect the metabolism of lipoproteins, such as diabetes mellitus (diabetic dyslipidemia) and chronic renal insufficiency (renal dyslipidemia) (Khavandi et al., 2017; Schofield et al., 2016; Taskinen and Borèn, 2015; Vergès, 2015; Wu and Parhofer, 2014; Chehade et al., 2013; Ng, 2013; Caron et al., 2012; Mooradian, 2009; Goldberg, 2001). High plasma levels of TG (> 150 mg/dL) and low levels of HDL-C (< 40 mg/dL in men and < 50 mg/dL in women) are found in about two thirds of T2DM (Arca et al., 2012). The prevalence of diabetic dyslipidemia varies widely, ranging from 37% to as high as 85% (Schofield et al., 2016; Taskinen and Borèn, 2015). These lipid abnormalities are associated with increased cardiovascular risk in T2DM patients. Recently, emphasis has been placed on the role of ApoCIII in diabetic dyslipidemia of T2DM patients (Wu and Parhofer, 2014; Jin et al., 2016; Avall et al., 2015; Qamar et al., 2015; Caron et al., 2011; Florez et al., 2006; Attman and Samuelsson, 2009; Hiukka et al., 2005; Adiels et al., 2005; Vergès et al., 2000). It was demonstrated that local ApoCIII production is linked to pancreatic islet insulin resistance and β cell failure in T2DM; thus, locally produced ApoCIII may serve as an important diabetogenic factor involved in the impairment of β cell function (Avall et al., 2015). It has also been suggested that increased ApoCIII levels may contribute to diabetic dyslipidemia in subjects with insulin resistance through its effects on TG and LDL particle size (Florez et al., 2006). It is believed that an increased concentration of atherogenic ApoCIII is the hallmark of renal dyslipidemia and may result from disturbance of insulin metabolism (Attman and Samuelsson, 2009). Evidence has shown that the concentration of VLDL₃ is significantly increased in T2DM patients (Hiukka et al., 2005), and VLDL₃ with a higher TG content exhibited abundant ApoCIII (Adiels et al., 2005). As a result, it is proposed that overproduction of VLDL₃ is a dominant feature of diabetic dyslipidemia in T2DM (Adiels et al., 2005). Furthermore, evidence from genetic studies of loss of function mutations in ApoCIII and a null mutation in human ApoCIII have led to the development of new lipid-lowering drugs via antisense oligonucleotides (ASOs) treatment (Luo and Peng, 2016; Visser et al., 2012). Recently, ASOs (e.g., lomitapide, mipomersen, proprotein convertase subtilisin/kexin-9 inhibitors) have emerged as promising new lipid-lowering agents (Visser et al., 2012). More recently a clinical trial showed that a second-generation inhibitor of ApoCIII, 2′-O-methoxethyl chimeric ASO volanesorsen, improves diabetic dyslipidemia, insulin sensitivity and hyperglycemia in T2DM patients.
Our previous work has described treatment of severe hypertriglyceridemia, hyperchylomicronemia, and TG-rich-lipoprotein (TRL) remnant excess with volanesorsen (Rocha et al., 2017). Herein, this paper will review recent advances concerning the pathophysiology of diabetic dyslipidemia in T2DM, the pathological role of ApoCIII in diabetic dyslipidemia, and a newly developed ApoCIII inhibitor volanesorsen for treatment of T2DM patients.

2. Pathophysiology of diabetic dyslipidemia in T2DM

Insulin resistance, adipocytokines (adiponectin or retinol-binding protein 4), hyperglycemia and obesity are likely to contribute to diabetic dyslipidemia (Schofield et al., 2016; Vergès, 2015), however; the pathophysiology is not fully understood. Verge (Vergès, 2015) proposed that the sequences of lipid events leading to diabetic dyslipidemia may be described as (1) quantitative lipoprotein abnormalities, (2) qualitative lipoprotein abnormalities, and (3) kinetic abnormalities. The quantitative lipoprotein abnormality is characterized by increased plasma concentration of TG and decreased HDL-C levels. The dominant features of the qualitative lipoprotein abnormalities are the increased large, very-low-density lipoprotein 1 (VLDL1) and small, dense LDL (sdLDL) as well as increased triacylglycerol content of LDL and HDL (Fig. 1). Finally, the kinetic abnormalities consist mainly of increased production of VLDL1, decreased VLDL catabolism and increased HDL catabolism. Amongst the five distinct major classes of lipoproteins (i.e., chylomicrons, VLDL, IDL, LDL, HDL), VLDL1 has become the main focus regarding the pathophysiology of diabetic dyslipidemia.

Hepatocyte-derived lipids enter the circulation as VLDL2. Large TG-rich VLDL1 particles are formed through two steps within the endoplasmic reticulum and Golgi complex from the primordial VLDL particle (pre-VLDL) to a TG-poor VLDL2 particles. Afterwards, VLDL2 can further be converted into VLDL1. The residence time of circulating VLDL1 and VLDL2 is determined by the activity of LPL. Once triglycerides are removed from VLDL1 though LPL-mediated lipolysis, they become VLDL2. VLDL1 particles contain more TG than VLDL2 particles and are abundant in ApoCIII and ApoE (Fig. 1). The production rate of VLDL1 correlates well with insulin resistance and increased liver fat content in T2DM. Insulin resistance is responsible for the increased activity of two factors, phospholipase D1 and ADP ribosylation factor 1, that are involved in the formation of VLDL1 (Taskinen and Borèn, 2015; Vergès, 2015). A study by Adiels and colleagues (Adiels et al., 2005) showed that VLDL1 metabolism is profoundly dysregulated in T2DM and that overproduction of VLDL particles in T2DM occurs mainly due to enhanced secretion of VLDL1ApoB100/VLDL1TG, not VLDL2. The increased VLDL1 in T2DM may be a consequence of hyperglycemia and high free fatty acid (FFAs) levels under conditions of insulin resistance (Taskinen and Borèn, 2015; Vergès, 2015). Hyperglycemia acts as a driving force to aggravate overproduction of VLDL1, while FFAs function as an inducer to increase VLDL1 production since hepatic fatty acid availability regulates VLDL-TG production. The apparent association of insulin resistance with increased production of VLDL1 has led to a view that the overproduction of VLDL1 is a dominant feature of diabetic dyslipidemia. This view is currently held by Taskinen, Borèn (Taskinen and Borèn, 2015) and Verge (Vergès, 2015) in their reviews.

VLDL1 also has a role in altering the composition of HDL. The alteration of HDL happens through the actions of cholesterol ester trans...
3. Role of ApoCIII in diabetic dyslipidemia of T2DM

3.1 Overview of ApoCIII

The human ApoCIII gene is expressed in the liver and intestine. ApoCIII is synthesized to a large extent by the liver and to a lesser extent by the intestine. ApoCIII mainly resides on ApoB-containing lipoproteins (chylomicrons, chylomicron remnants, VLDL, IDL, and LDL) but is also present on HDL particles. In normal conditions, about half to two-thirds of VLDL and IDL particles and about 10% of LDL particles have ApoCIII (Kawakami and Yoshiida, 2009). ApoCIII-rich VLDL or LDL particles are also abundant in ApoE. In subjects with normal triglyceride concentration, under the fasting state, ApoCIII is mostly present in HDL particles, whereas in the fed state, ApoCIII is transferred to chylomicron and VLDL particles (Kawakami and Yoshiida, 2009). In subjects with hypertriglyceridemia, the majority of ApoCIII is found in VLDL during fasting. When ApoCIII is present on chylomicron and VLDL it inhibits their uptake by the hepatocytes, leading to a decrease in catabolism and clearance of TG-rich lipoproteins (TRLs) (Kawakami and Yoshiida, 2009).

HDL can be divided into two subgroups according to the presence or absence of ApoCIII. ApoCIII-rich HDL cannot reduce the adhesion of monocytes to vascular endothelial cells, whereas HDL without ApoCIII decreases the adhesion. Therefore it is suggested that ApoCIII in HDL counters the anti-inflammatory and antiatherogenic property of HDL. (Kawakami and Yoshiida, 2009). It is likely that ApoCIII in HDL may also attenuate the anti-diabetogenic property of HDL in T2DM and the HDL dysfunction in T2DM is caused by the increased ApoCIII.

There are three major glycoforms of APOCIII: ApoCIIIa, ApoCIIIb, and ApoCIIIc. Koska and colleagues (Koska et al., 2016) found that ApoCIIIa and ApoCIIIb, but not ApoCIIIc, were associated with fasting plasma triglyceride levels in T2DM. Recent evidence has emerged to show that ApoCIIIa and ApoCIIIb, but not ApoCIIIc, were associated with the formation of small dense LDL (Mendoza et al., 2017).

3.2 ApoCIII inhibits lipoprotein lipase

ApoCIII is a powerful inhibitor of lipoprotein lipase (LPL) and reduces ApoE-mediated hepatic uptake of triglyceride-rich lipoproteins (TRLs) remnants. The impaired lipolysis by inhibition of LPL and hepatic lipase may contribute to diabetic dyslipidemia. Insulin resistance is likely to be linked to ApoCIII synthesis and release, since ApoCIII is upregulated in insulin-deficient status and suppressed by the administration of insulin (Attman and Samuelsson, 2009). Therefore, it is believed that the marked increase in ApoCIII-containing triglyceride-rich lipoproteins is a major feature of diabetic dyslipidemia. (Wu and Parhofer, 2014; Chehade et al., 2013; Ng, 2013; Arca et al., 2012; Moordadian, 2009; Goldberg, 2001; Jin et al., 2016; Florez et al., 2006; Attman and Samuelsson, 2009).

Some apolipoproteins can function as inhibitors or activators of LPL-mediated lipolysis, act as modulators of LPL action in chylomicron remnants, and serve as a mediator of chylomicron and hepatic lipase uptake in the liver. For example, lipolysis can be activated by ApoCIII and stimulated by ApoA5, whereas it is inhibited by ApoCIII and angiopoietin-like proteins (ANGPT3 and ANGPTL4). Apolipoproteins can also act as a modulator in the action of chylomicron clearance. In the process of chylomicrons converting into the chylomicron remnants via LPL-mediated lipolysis, chylomicron remnants acquire ApoE from HDL particles. Furthermore, ApoE interacts with the hepatic LDL receptors and the interaction results in chylomicron remnants in the liver. ApoCIII and ApoCIII can each modulate chylomicron clearance into the liver by interfering with the biding of ApoE to its receptors (Khavandi et al., 2017; Taskinen and Borén, 2015; Vergès, 2015).

3.3 Relationship between ApoCIII and insulin resistance

Avall and colleagues (Avall et al., 2015) demonstrated that in T2DM the local ApoCIII production is linked to pancreatic islet insulin resistance and β cell failure, resulting in increased local inflammation, increased mitochondrial metabolism, derangement of free calcium (Ca²⁺) concentration in the cytoplasm of β cells and induction of β cell apoptosis and progressive β cell loss. Therefore it is suggested that under conditions of islet insulin resistance, locally produced ApoCIII is an important diabetogenic factor (Avall et al., 2015). Qamar and colleagues (Qamar et al., 2015) found a significant positive relationship between ApoCIII levels and fasting glucose as well as glycosylated hemoglobin A1C (HbA1C) in T2DM. They also...
demonstrated a strong positive relationship between plasma ApoC-III and TG, total cholesterol, ApoB and ApoE levels and a negative relationship between HDL-C and ApoA1 levels. Caron and colleagues (Caron et al., 2011) showed that ApoCII gene expression is increased by glucose stimulation which leads to the idea that transcriptional activation of ApoCII expression by glucose is likely to contribute to diabetic dyslipidemia. Florez and colleagues (Florez et al., 2006) found an inverse relationship between ApoCII levels and small dense LDL particles in T2DM, indicating a direct effect of ApoCII on the clearance of TRL and the production of smaller LDL particles. Hukka and colleagues (Hjukka et al., 2005) found that the increase of VLDL also exacerbates insulin resistance status (diabetes. ApoCIII is not only induced by insulin resistance, but thus resulting in elevated plasma ApoCIII in T2DM (insulin resistance increases the expression and secretion of ApoCIII, involving disturbances of ApoCIII and ApoE metabolism. In addition, ApoE level were decreased in T2DM. They postulate that the rise in VLDL triglycerides is a key feature of diabetic dyslipidemia and involves disturbances of ApoCIII and ApoE metabolism. In addition, insulin resistance increases the expression and secretion of ApoCII, thus resulting in elevated plasma ApoCII in T2DM (Kawakami and Yoshida, 2009). Interestingly, Kawakami and Yoshida (Kawakami and Yoshida, 2009) put forward a mechanism by which ApoCIII causes insulin resistance in vascular endothelial cells. On the basis of their findings ApoCII in TG-rich lipoproteins (TRLs) impairs insulin signaling in vascular endothelial cells, therefore, ApoCIII is likely the link between dyslipidemia and endothelial dysfunction (Fig. 2). In contrast to the generally accepted idea that insulin resistance increases the expression and secretion of ApoCII, Kawakami and Yoshida’s hypothesis is that a vicious cycle is formed between the primary event of insulin resistance leading to ApoCII increment and a secondary event of ApoCIII aggravating insulin resistance, leading to diabetic dyslipidemia. In summary, ApoCIII exerts pro-atherogenic and pro-diabetogenic effects (Kawakami and Yoshida, 2009; Galton, 2017; Caron, 2008), and it’s a major contributor to diabetic dyslipidemia. ApoCII is not only induced by insulin resistance, but also exacerbates insulin resistance status (Kawakami and Yoshida, 2009).

4. Volanesorsen for treatment of diabetic dyslipidemia

Volanesorsen (ISIS 304801) is a second-generation 2′-O-methoxyethyl chimeric ASO designed to sequence-specifically reduce expression levels of the human ApoCIII mRNA, thus enhancing LPL activity. Volanesorsen was studied in a randomized, double-blind, placebo controlled trial with 15 patients with T2DM (HbA1c > 7.5% [58 mmol/mol] and TG > 200 and < 500 mg/dL) in order to determine the effects of volanesorsen on TG and insulin resistance (Digenio et al., 2016). Patients randomized to the treatment arm (n = 10) received volanesorsen 300 mg/week, sc., and placebo (n = 5) for 15 weeks. This resulted in significantly reduced plasma levels of TG (-69%, p = 0.02) and increased levels of HDL-C (43%, p = 0.03). The therapeutic efficacy of volanesorsen on TG and HDL-C was accompanied by decreased plasma levels of ApoCII (-88%, p = 0.02) and improvement of insulin sensitivity (57%, p < 0.001) and no significant changes of HDL-C (p = 0.706) (Digenio et al., 2016). The most common adverse events were local cutaneous reaction at the injection site (15% of all injections), followed by upper-respiratory tract infection (5 patients, 50%) and headaches (5 patients, 50%) (Digenio et al., 2016). This study as well as other previous studies (Graham et al., 2013; Gaudet et al., 2015; Yang et al., 2016; Gaudet et al., 2014, 2015; Gouni-Berthold et al., 2017) demonstrate that volanesorsen exerts anti-atherogenic and anti-diabetogenic effects in patients with lipid abnormalities. Furthermore, this study demonstrated that volanesorsen resulted in a statistically significantly reduction of VLDL-ApoCII (-90%, p = 0.023) at the end of treatment (day 91). This finding may indicate that the reduced plasma levels of TG are mainly from TG-rich VLDL, but not from sDLDL (cholesterol ester-poor LDL) because there were no changes of HDL-C before and after treatment with volanesorsen. Additionally, treatment with volanesorsen led to a significant increase of HDL-C (43%, p = 0.034), indicating that volanesorsen may change the ratio of TG-rich HDL2: TG-poor HDL4, thus enhancing HDL levels and facilitating restoration of HDL function (see Fig. 1). Interestingly, this study also showed that % change of ApoB levels was not significantly changed at day 91 compared baseline levels (p = 0.27). These findings may have implications in the efficacy of volanesorsen since ApoB increases hepatic triglyceride (Schofield et al., 2016). The above-cited data led Digenio and colleagues (Digenio et al., 2016) to conclude that inhibition of ApoCIII with volanesorsen could result in robust suppression of TG that may benefit to T2DM patients. Many review articles have described lipid lowering agents for treatment of diabetic dyslipidemia (Khavandi et al., 2017; Schofield et al., 2016; Wu and Parhofer, 2014; Chehade et al., 2013; Ng, 2013; Mooradian, 2009). However, limited data are available on the comparison of volanesorsen to other agents. Chehade and colleagues (Chehade et al., 2013) provided detailed information about therapeutic agents available (as of 2013) for the management of dyslipidemia (Fig. 3). The percentage of reduction in TG levels, in descending order, is 69% by volanesorsen, 20-50% by niacin, 20-50% by fibrates, 7-30% by statins, 25-30% by omega-3 fatty acid, 8% by ezetimibe, 10% (possible increase) by bile acid binding agents. On the other hand, the percentage increase in HDL-C levels, in ascending order, is 42% by volanesorsen, 10-35% by fibrates, 15-35% by niacin, 5-15% by statins, 1-10% by omega-3 fatty acids, and 1% by ezetimibe (Chehade et al., 2013). Atorvastatin was shown reduce TG by 25% to 35% and ApoB levels by 31% to 40% (10 mg and 80 mg, respectively) in 217 patients with T2DM (Diabetes Atorvastin Lipid Intervention Study Group, 2001). The Diabetes Atorvastin Lipid Intervention Study Group (DALI) originally proposed that the mechanism by which atorvastatin lowers plasma TG levels is likely due to an effect on hepatic TG secretion, with no effect on LPL, as it was found to be at normal range in their study (Diabetes Atorvastin Lipid Intervention Study Group, 2001). However, their study subsequently showed a significant reduction in ApoCII and ApoB containing lipoproteins (Dallinga-Thie et al., 2004). Studies have demonstrated that, in addition to the known upregulation of LDL receptors, statins are also able to reduce triglyceride levels and suppress ApoCII (Ng, 2013; Kei et al., 2013; Rjpathak et al., 2009; Sattar et al., 2010). Interestingly, Zheng and colleagues (Zheng et al., 2013) demonstrated that statins (atorvastatin, pitavastatin, and pravastatin) suppress ApoCII-induced vascular endothelial activation and monocyte adhesion.
Figure 3. Effects of drug or drug class on TG and HDL-C in T2DM. The effects of statins (HMG-CoA reductase inhibitors) are based on the data of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin. The effects of ezetimibe are based on the data of Zetia® (Merck & Co., Inc, Whitehouse Station, NJ) and Ezetrol® (EU). The effects of fibrates (fibric acid derivatives) are based on the data of fenofibrate, gemifibrozil, bezafibrate, and bezalip. The effects of bile acid binding agents are based on the data of cholestyramine, colestipol, and colesevelam. The effects of omega-3 fatty acids are based on the data of Lovaza® (omega-3-acid ethyl esters) (GlaxoSmithKline, Research Triangle Park, NC), and Pure EPA Vascepa® (icosapent ethyl) (Amarin Pharma Inc., Bedminster, NJ), and some over-the-counter (OTC) agents.

The possible effect of statin therapy on incident diabetes have emerged in one meta-analysis (a small increase in diabetic risk with PR 1.13 [95% CI, 1.03-1.23]) (Rjpathak et al., 2009). and in another meta-analysis (a 9% increased risk for incident diabetes, odds ration 1.09; 95% CI 1.02-1.17) (Sattar et al., 2010). However, it is probable that the detrimental effects will be offset by the beneficial effects of statins. Kei and colleagues (Kei et al., 2013) showed that rosuvastatin monotherapy and add-on ER-NA (nicotinic acid)/LRPT (laropiprant) groups were associated with 56% and 24% reduction in high-sensitivity C-reactive protein levels (p < 0.01 compared with baseline), but add-on fenofibrate did not result in the beneficial effects. Therefore, treatment of patients with mixed dyslipidemia with highest dose rosuvastatin may result in more pronounced beneficial modifications in emerging cardiovascular risk factors (Kei et al., 2013). The mechanisms by which statins increase the risk of T2DM are unclear, but it is likely to relate to statin-induced insulin resistance in adipose tissue and adipocytes (Henriksen et al., 2014).

Interestingly, fibrates also reduce ApoCIII and activate LPL activity (Ng, 2013). However, when added on to rosuvastatin, fenofibrate was found to confer a modest 4% reduction in ApoB levels (Kei et al., 2013). Extended-release niacin increases HDL ApoA1 concentration in statin-treated subjects with T2DM by lowering ApoA1 fractional catabolic rate (Pang et al., 2014). Niacin is thought to have a moderate effect on lowering LDL-C, triglyceride and lipoprotein (a) (Wu and Parhofer, 2014). However, niacin as add-on therapy to statins did not yield additional beneficial effects when compared with statin monotherapy (AIM-HIGH et al., 2011; HPS2-THRIVE Collaborate Group, 2013).

Despite an initial support from the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), in 2018, the new drug application of volanesorsen for familial chylomicronemia syndrome (FCS) was rejected by the US Food and Drug Administration due to concerns for serious bleeding and thrombocytopenia. It is unclear whether this decision will be reconsidered in the future for FCS or other conditions associated with significantly elevated triglyceride levels such as diabetic dyslipidemia.

5. Conclusions
Changes in VLDL, sdLDL, and HDL2 induced by insulin resistance underlie diabetic dyslipidemia. ApoCIII exerts proatherogenic and pro-diabetogenic effects and is a major contributor to this condition. ApoCIII is not only induced by insulin resistance, but also exacerbates insulin-resistant status. Given the current evidence discussed in this review, volanesorsen is a promising therapy for the treatment of diabetic dyslipidemia.

Conflict of interest
The authors declare no competing interests.

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