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Platelet Function Profiles in Patients with Diabetes Mellitus

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Abstract Patients with diabetes mellitus (DM) are at high risk for several cardiovascular disorders such as coronary heart disease, stroke, peripheral arterial disease, and congestive heart failure. DM has reached epidemic proportions and its strong association with coronary artery disease is responsible for increased cardiovascular morbidity and mortality. DM patients are characterized by platelet hyperreactivity, which contribute to the enhanced atherothrombotic risk of these subjects. Several mechanisms are involved in the hyperreactive platelet phenotype characterizing DM patients. Furthermore, a large proportion of DM patients show inadequate response to standard antiplatelet treatments and high rate of adverse recurrent cardiovascular events despite compliance with standard antiplatelet treatment regimens. Therefore, new antiplatelet treatment regimens are warranted in DM patients to reduce their atherothrombotic risk. The present manuscript provides an overview on the current status of knowledge on platelet function profiles in patients with DM and therapeutic considerations.

Keywords Diabetes mellitus · Platelets function · Cardiovascular disease

Type 2 diabetes mellitus (DM) is a complex disease, diagnosed in approximately two million persons each year in the USA and worldwide its prevalence continues to climb [1]. Patients with DM have accelerated atherosclerosis, high risk of cardiovascular disease as well as atherothrombotic complications [2, 3]. Notably, DM patients without a history of coronary artery disease (CAD) have overall the same cardiac risk as non-DM patients with a history of myocardial infarction (MI) [4]. Furthermore, the presence of DM in the setting of an acute coronary syndrome (ACS), presenting with and without ST elevation, is a strong independent predictor of short-term and long-term recurrent ischemic events, including mortality [5, 6]. Several investigations have shown that DM subjects are characterized by prothrombotic status which is attributed to numerous factors, including a pro-coagulant status, impaired fibrinolysis, endothelial dysfunction, and increased platelet reactivity. The latter is a result of multiple causes which ultimately cause dysregulation of several platelet signaling pathways leading to a hyperreactive platelet phenotype [2, 7–11] (Table 1). This may contribute to another important feature of DM which consists in an impaired response to standard antiplatelet therapy which may also explain the worse outcomes found in DM subjects when compared with non-DM subjects [9, 12, 13]. The present manuscript provides an overview on the current status of knowledge on platelet function profiles in patients with DM and therapeutic considerations.

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Platelet Abnormalities in DM Patients: Mechanisms

Several studies underscore the pivotal role of platelets in atherosclerosis and its thrombotic complications [14, 15]. The intensified adhesion, activation, aggregation, and platelet-derived thrombin generation are all abnormalities which characterize DM platelets [2, 7–11] (Table 1). These findings can be attributed to several factors. In particular, it is possible to identify different metabolic and cellular mechanisms closely interrelated, which can be grouped into the following categories: hyperglycemia, insulin resistance, associated metabolic conditions and other cellular abnormalities (Fig. 1) [12].

Hyperglycemia

Diabetes is a metabolic condition characterized by dysfunction in insulin secretion and insulin action resulting in

Table 1 Platelet abnormalities in patients with diabetes mellitus [2, 7–11]

Increased adhesion and activation
Amplified agonist-receptor coupling
Increased capacity for prostanoid generation
Decreased capacity for NO− generation
Enhanced generation of reactive oxygen species
Resistance to NO− and prostacyclin
Increased cytosolic calcium mobilization
Increased α-granule content with concomitantly increased release
Increased platelet volume
Increased numbers of glycoprotein receptors GPIb and GPIIb/IIIa
Increased membrane protein glycation
Altered membrane fluidity
Increased binding of adhesive RGD-protein ligands (e.g., fibrinogen)
Increased content and release of plasminogen activator inhibitor-1

RGD arginine–glycine–asparagine, *NO* nitric oxide, *GPIIb/IIIa* glycoprotein IIb/IIIa

chronic hyperglycemia and deeply affecting the cardiovascular system. Hyperglycemia per se may play an independent role in the abnormalities found in platelets of DM patients [16], in particular hyperglycemia has been identified as a causal factor for in vivo platelet activation and platelet hyperreactivity [16, 17]. DM platelets are characterized by enhanced thromboxane biosynthesis, enhanced expression of adhesion molecules and activation markers [18]. Several investigations have reported different mechanisms to explain increased platelet reactivity in hyperglycemia status. These include: (1) glycation of platelet surface proteins decreases membrane fluidity, increases platelet adhesion and thus causes incorporation of glycated proteins into thrombi [19–21]; (2) activation of protein kinase C, a mediator of platelet activation, through an increased production of the lipid second messenger diacylglycerol [22, 23]; (3) increased intracellular calcium concentration due to glycation of circulating low-density lipoproteins (LDL) [24]; (4) decreased production of endothelium-derived nitric oxide (NO), which impairs endothelium-dependent vasodilation [25]; (5) production of reactive oxygen species [26]; (6) platelet glycoprotein (GP) IIb/IIIa and P-selectin expression activated by osmotic effect of glucose [27]. In addition, hyperglycemia inhibits fibrinolysis by increasing concentrations of plasminogen activator inhibitor [28] and promoted coagulation by raising concentrations of procoagulant factors (e.g., tissue factor, von Willebrand factor) [29, 30].

Studies have shown that a decrease in expression of platelet activation markers after improved metabolic control [31]. Even clinical studies investigated the effects of glucose-lowering therapy in patients with DM in the acute setting [32]. Moreover, there are the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) and DIGAMI-2 trials. In the DIGAMI standard treatment plus insulin-glucose infusion for 24 h followed by multidose insulin therapy was superior to standard treatment alone in the mortality at 3.4 years (33 vs. 44 %; RR=0.72; p=0.011) [33]. However, in the DIGAMI-2 trial no significant differences in mortality, non-fatal reinfarction or stroke were found among three glucose-lowering strategies (group 1: glucose–insulin infusion titrated by glucose levels at least for 24 h followed by insulin-based long-term glucose control; group 2: glucose–insulin infusion titrated by glucose levels at least for 24 h followed by standard glucose control; and group 3: routine metabolic control according to local practice), which achieved similar glucose levels [34]. These results suggest that the benefit of decreasing glucose levels is independent of the way it is achieved. Moreover, the optimal blood glucose concentration for events reduction remains still unknown. In fact, the ACCORD (Action to Control Cardiovascular Risk in Diabetes Study Group) trial suggested that an excessive glucose lowering may be even dangerous. The trial, which randomized 10,251 DM patients to receive an intensive glucose-lowering regimen (glycated hemoglobin level <6.0 % as target) or a standard treatment (targeting a glycated hemoglobin level 7.0–7.9 %) had to be interrupted prematurely after 3.5 years of follow-up due to greater rate of mortality in the intensive regimen group [35]. The NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) trial showed similar results. In fact, patients randomized to undergo intensive glucose control (target blood glucose range 4.5 to 6.0 mmol/l) showed higher mortality than patients on conventional glucose control (target of 10.0 mmol/l or less) [36].

Insulin Resistance and Deficient Secretion

Differences in platelet abnormalities can be attributed to the different mechanisms contributing to the DM status. In fact, type 1 DM (5–10 % of cases) is caused by a cellular-mediated autoimmune destruction of the pancreatic β-cells, resulting in an absolute deficiency of insulin secretion, while type 2 DM (90–95 %) is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (relative insulin deficiency) [37]. Deficient insulin action strongly contributes to platelet dysfunction. Platelets express both insulin receptors (IR) and insulin-like growth factor-1 (IGF-1) receptors [38, 39] and the binding of insulin to platelets increases also surface expression of adenylate cyclase-linked prostacyclin receptor [40]. Nevertheless, IR expression is relatively low because the majority of its subunits heterodimerize with those of the IGF-1 receptor to form an insulin/IGF-1 hybrid receptor, which avidly binds IGF-1 but not insulin [39]. The presence of IGF-1 in the granules of platelets and the expression of its

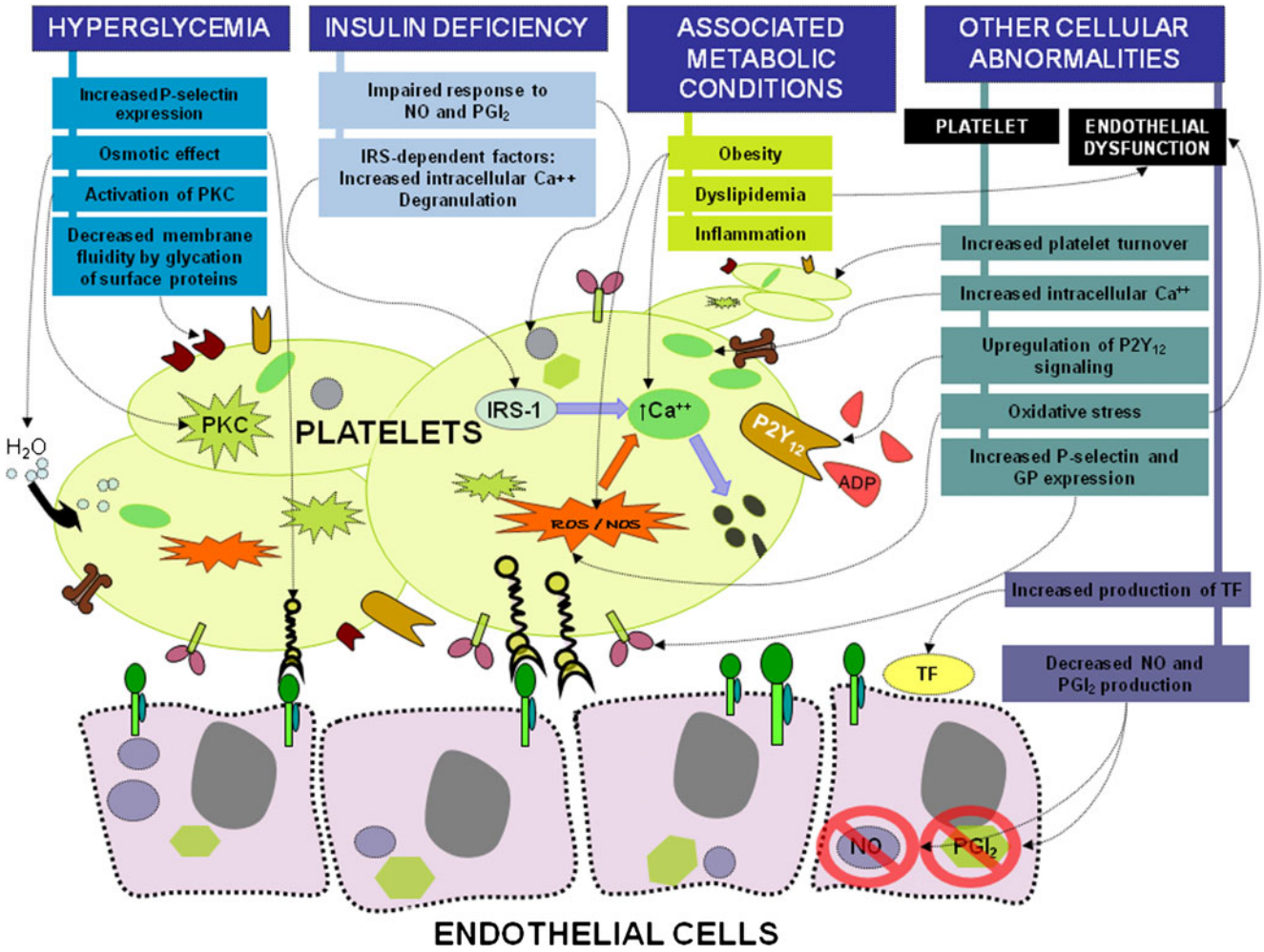

Fig. 1 Mechanisms of platelet dysfunction in patients with diabetes mellitus, Mechanisms contributing to platelet dysfunction in diabetes mellitus (DM) patients, including hyperglycemia, insulin deficiency, associated metabolic conditions, and other cellular abnormalities. *ADP*: adenosine diphosphate; *CA^{++}*: calcium; *GP*: glycoprotein; *IRS*: insulin receptor substrate; *NO*: nitric oxide; *PGI_2*: prostacycline; *PKC*: protein kinase C; *ROS/NOS*: reactive oxygen and nitrogen species; *TF*: tissue factor

receptor on platelets surface may contribute to the amplification of platelet responses and to the pathogenesis of cardiovascular disease. The functional and signaling pathways involved in IGF-1 modulation of platelet reactivity, however, are currently not completely known [18].

Abnormalities in insulin-mediated signaling pathways, which contribute to the hampered or abolished platelet-inhibitory effect in patients with insulin resistance, can be classified in insulin receptor substrate (IRS)-dependent and independent factors [18, 41, 42]. Angiolillo et al. showed that genetic variations of IRS-1 are associated with different patterns of platelet function profiles and can identify type 2 DM patients with a hyperreactive platelet phenotype. Notably, these patients are also at an increased risk of adverse cardiovascular events [43]. Among IRS-dependent factors, insulin resistance provokes an increase in intracellular calcium concentration, leading to enhanced platelet degranulation and aggregation [44], with a mechanism not yet fully clear. IRS-independent pathways include the reduction of platelet sensitivity to NO and prostacyclin (PGI_2) which are released by the endothelium and hamper platelet activation. Therefore, an impaired response to these molecules contributed to a hyperreactive platelet phenotype [45, 46]. Moreover, restoration of platelet sensitivity to NO and PGI_2 has been correlated with the improvement of insulin sensitivity [47]. This may contribute to the suggested benefits of thiazolidinediones, characterized by potent insulin sensitizing effects, on platelet function. In fact, an enhanced sensitivity to NO and partial normalization of intracellular calcium concentrations in DM patients [48], and a diminished P-selectin expression in non-DM patients with CAD has been observed while rosiglitazone treatment [49]. In the multicenter randomized PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) trial pioglitazone (an insulin sensitizer) was associated with a reduced atherosclerotic

disease progression measured by intravascular ultrasonography compared with glimepiride (an insulin secretagogue) at 18 months in patients with type 2 DM and stable CAD (n=543) [50]. In the post hoc analysis of the SIMPHONY (Sibrafiban vs Aspirin to Yield Maximun Protection from Ischemic Heart Events Post-acute Coronary Syndromes) and SIMPHONY-2 trials, therapy with biguanide and/or thiazolidinedione was associated with lower cardiovascular events at 90 days compared with insulin-providing treatment with insulin and/or sulfonylurea in DM patients after an ACS (n=3,101) [51]. However, these results were not confirmed in the APPROACH (Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients with Cardiovascular History) trial [52]. Recently, Suryadevara et al. reported pharmacodynamic (PD) data about the impact of pioglitazone on clopidogrel-mediated $P2Y_{12}$ inhibitory effects in patients with type 2 DM. In this prospective, randomized, double-blind, placebo-controlled, cross-over PD study, the adjunctive use of pioglitazone does not result in enhanced platelet inhibition [53].

Metabolic Conditions Associated with DM

Metabolic conditions such as obesity, dyslipidemia, and enhanced systemic inflammatory status are commonly associated with type 2 DM and may contribute to the hyperreactive platelet phenotype observed in this population. Obesity is frequently associated with insulin resistance [18], elevated platelet count and high mean platelet volume [54], higher serum leptin concentration [55], greater cytosolic free calcium concentration [56], and increased oxidative stress [57]. Of note, in a population of subjects affected with central obesity, diet-induced weight loss showed to restore the sensitivity to NO and PGI_2 and reduce platelet activation [47]. Likewise, in subjects with elevated body mass index response to antiplatelet drugs such as clopidogrel is also impaired [58–60]. Dyslipidemic patients present high levels of triglycerides and low levels of high-density lipoprotein (HDL) cholesterol [18]. Triglyceride-rich very-low-density lipoprotein (VLDL) particles impair fibrinolysis and affect coagulation cascade predisposing to atherothrombosis [61]. Hypertriglyceridemia is also known to induce platelet activation with a mechanism based on the interaction between the apoE content of VLDL particles and the platelet LDL receptor [62]. Low concentrations of HDL are associated with endothelial dysfunction [63] and recently Calkin et al. showed a reduction of platelet aggregation in a DM cohort after administration of reconstituted HDL, with a mechanism mediated by cholesterol efflux from platelets. Patients with DM have also increased systemic inflammation and platelets activation and coagulation markers compared to healthy subjects [64].

Other Cellular Abnormalities

Dysregulation of calcium metabolism, oxidative stress, upregulation of $P2Y_{12}$ signaling pathway and accelerated platelet turnover are commonly present in DM patients and may contribute to the platelet hyperreactivity status. Although the exact mechanisms are not known, the increased cytosolic calcium concentration, due to impaired regulation of calcium metabolism, characterizes platelets of patients with DM. The suggested mechanisms include augmented influx of calcium through the sodium/calcium exchanger [65], altered activity of calcium ATPase [66], reduced sensitivity to insulin that diminishes sarcoplasmic reticulum calcium-ATPase (SERCA-2) [41, 48], and augmented oxidative stress, which enhances calcium signaling through increased formation of superoxide anions and reduced nitric oxide production [67]. This increased cytosolic calcium concentration creates an enhanced platelet reactivity [41, 68]. DM is associated with an overproduction of reactive oxygen and nitrogen species, as well as with reduced platelet antioxidant levels which enhance platelet activation [68–72]. The increased production of reactive oxygen species is associated with more production of advanced glycation end products (AGEs) [73], which cause atherosclerotic complications by increasing platelet aggregation through the serotonin receptor [74] and activating the receptor for AGEs [75]. In addition, oxidative stress contributes to endothelial dysfunction and thus to the prothrombotic status, which characterize DM, through an increased production of tissue factor [76, 77]. Ultimately, patients with DM are characterized by a higher number of reticulated platelets, a marker of elevated platelets turnover, which results in greater platelet reactivity [78].

Antiplatelet Therapy and Platelet Functional Profile in Patients with Diabetes Mellitus

Currently, three different classes of antiplatelet drugs are available for treatment and prevention of ischemic complications in patients with CAD: cycloxigenase-1 (COX-1) inhibitors (aspirin), GP IIb/IIIa inhibitors and adenosine diphosphate (ADP) $P2Y_{12}$ receptor antagonist (Table 2). Therapy with GP IIb/IIIa inhibitors is reasonable in high-risk ACS patients undergoing PCI, which obviously include those with DM [79]. However, the use of these drugs is associated with increased risk of bleeding. Recent studies have demonstrated that bivalirudin is as effective as conventional therapy with heparin and GP IIb/IIIa inhibitors with a better safety profile in DM patients [80] and thus may be considered an important therapeutic option in this high-risk setting. The use of antithrombotic treatment strategies for acute use goes beyond the scope of this review,

Table 2 Pharmacology of key antithrombotic medications used in patients with coronary artery disease

Name	Class	Molecular target	Type of binding	Dosage	Route of administration	References
Aspirin	NSAIDs	COX-1	Irreversible	162–325 mg LD 500 mg LD (IV) 75–162 mg/day MD	Oral IV	79, 87, 88
Clopidogrel	Thienopyridine	ADP $P2Y_{12}$ receptor	Irreversible	300–600 mg LD 75 mg/day MD	Oral	99–101
Prasugrel	Thienopyridine	ADP $P2Y_{12}$ receptor	Irreversible	60 mg LD 10 mg/day MD	Oral	145
Ticagrelor	Cyclopentyltriazolo-pyrimidine	ADP $P2Y_{12}$ receptor	Reversible	180 mg LD 90 mg twice/day MD	Oral	150–153
Cangrelor	ATP analogue	ADP $P2Y_{12}$ receptor	Reversible	30-μg/kg bolus dose 4-μg/kg/min	IV	145, 156
Elinogrel	Quinazolinedione	ADP $P2Y_{12}$ receptor	Reversible	80 mg IV bolus 50, 100, or 150 mg twice/day MD	Oral IV	161–164
Cilostazol	Quinolinone derivative	Selective inhibitor of PDE3	Reversible	200 mg LD 100 mg twice/day MD	Oral	158, 165–169
Atopaxar	Thrombin receptor antagonist	PAR-1 receptor	Reversible	400 mg LD 50, 100, or 200 mg/day MD (phase II trials)	Oral	138
Vorapaxar	Thrombin receptor antagonist	PAR-1 receptor	Reversible	40 mg LD 2.5 mg/day MD	Oral	171, 172
Rivaroxaban	Anticoagulant	Factor Xa	Irreversible	2.5 mg twice/day MD	Oral	174

ADP adenosine diphosphate, *ATP* adenosine triphosphate, *COX* cyclooxygenase, *IV* intravenous, *LD* loading dose, *MD* maintenance dose, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PDE3* 3-type phosphodiesterase, *PAR-1* protease-activated receptor-1

which is focused on long-term secondary prevention antithrombotic treatment regimens. In particular, this section provides an overview on the benefits, limitations and short and long term outcome of oral antiplatelets agents in DM (Table 3).

Aspirin

Aspirin selectively acetylates cyclooxygenase-1 (COX-1), thereby blocking the formation of thromboxane A_2 (TXA_2) in platelets [81]. This effect is irreversible, as platelets are enucleate and thus are unable to resynthesize COX-1. The role of aspirin for primary prevention in DM patients is still controversial. The ETDRS (Early Treatment Diabetic Retinopathy Study) showed a significant decrease in the relative risk of MI at 5 years (RR=0.72; $p<0.01$) with aspirin (325 mg bid) in DM patients ($n=3,711$), although no significant difference in mortality was observed [82]. The POPADAD (Prevention of Progression of Arterial Disease and Diabetes) trial randomized patients ($n=1,276$) with type 1 or 2 DM over the age of 40 with asymptomatic peripheral artery disease to aspirin (100 mg) or antioxidants and did not show any benefit in primary prevention of cardiovascular events [83]. In the JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes) trial the use of aspirin (81 to 100 mg) for primary prevention of cardiovascular events showed a 20 % difference between the aspirin and non-aspirin arms in the primary endpoint (atherosclerotic events) but without achieving statistical significance [84]. Nevertheless, the incidence of fatal coronary and cerebrovascular events (a secondary endpoint) was significantly reduced. Several meta-analyses have been performed in order to reconcile the results obtained in the different trials and showed that aspirin produces only a modest reduction in cardiovascular events. Therefore, present guidelines do not recommend routine use of aspirin for primary prevention in DM patients [85]. A consensus from the American Diabetes Association, the American Heart Association and the American College of Cardiology Foundation recommends low-dose aspirin (75–162 mg/day) for primary prevention in adults with DM and no previous history of vascular disease who are at increased cardiovascular disease (CVD) risk (10-year risk of CVD events over 10 %) and who are not at increased risk for bleeding. Aspirin is also recommend for DM subjects who have increased CVD risk (men over age 50 years and women over age 60 years with one or more major risk factors) [86]. The ASCEND (A Study of Cardiovascular Events in Diabetes; NCT00135226) and ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes; ISRCTN48110081) trials are studying the role of aspirin in primary prevention in DM cohort.

Table 3 Pivotal antithrombotic trials in patients with coronary artery disease and diabetes mellitus

Study	*N* (DM/total population)	Study drugs	Setting	Endpoint	Outcomes in DM	Reference
ETDRS[a]	3,711/3,711	Aspirin vs placebo	Clinical diagnosis of DM	All cause mortality	RR 0.91 (CI 0.75–1.11)	82
POPADAD[a]	1,276/1,276	Aspirin, antioxidant or placebo	Type 1 or type 2 DM and an ankle brachial pressure index of ≤0.99	Death from coronary heart disease or stroke, non-fatal MI or stroke, or amputation above the ankle for critical limb ischemia	HR 0.98 (CI 0.76–1.26)	83
JPAD[a]	2,539/2,539	Low-dose aspirin vs placebo	Type 2 DM without a history of atherosclerotic disease	Any atherosclerotic events	HR 0.80 (CI 0.58–1.10)	84
CAPRIE	3,866/19,185	Aspirin + clopidogrel vs aspirin + placebo	Recent MI, stroke, and established PAD	Ischemic stroke, MI, or vascular death	15.6 % event rate/year vs 17.7 % event rate/year RR 2.1 %	103
CURE	2,840/12,562	Aspirin + clopidogrel vs aspirin + placebo	ACS	Cardiovascular death, nonfatal MI, or stroke at 1 year	14.2 vs 16.7 % RR 0.84 (CI 0.70–1.02)	105
PCI-CURE	504/2,658	Aspirin + clopidogrel vs aspirin + placebo	ACS undergoing PCI	Cardiovascular death, MI, or urgent TVR at 30 days	12.9 vs 16.5 % RR 0.77 (CI 0.48–1.22)	106
CREDO	560/2,116	Aspirin + clopidogrel vs aspirin + placebo	Elective PCI	Death, MI, or stroke at 1 year	% NA RRR 11.2 (CI 46.2 to −46.8)	107
PCI-CLARITY[b]	282/1,863	Aspirin+clopidogrel vs aspirin+placebo	STEMI with fibrinolysis	Cardiovascular death, recurrent MI, or stroke at 30 days	6.0 vs. 10.1 % OR 0.61 (CI 0.24–1.53)	110
CURRENT/OASIS-7	7,687/25,086	Clopidogrel double-dose, vs standard dose, and aspirin high dose vs standard dose	ACS and intended early PCI	Cardiovascular death, MI, or stroke at 30 days	HR 0.89 (CI 0.68–1.18) $P_{interaction}$=0.872 HR 1.12 (CI 0.85–1.48) $P_{interaction}$=0.216	135
TRITON-TIMI 38	3,146/13,608	Aspirin + prasugrel vs aspirin + clopidogrel	ACS undergoing PCI	Death from cardiovascular causes, nonfatal MI, or nonfatal stroke	12.2 vs 17 % HR 0.70 (CI 0.58–0.85) $P_{interaction}$=0.09	149
PLATO	4,662/18,624	Aspirin + ticagrelor vs aspirin + clopidogrel	ACS	Death from vascular causes, MI, or stroke	14.1 vs 16.2 % HR 0.88 (CI 0.76–1.03) $P_{interaction}$=0.49	155
CHAMPION-PCI	2,702/8,882	Cangrelor vs clopidogrel	Stable angina and ACS undergoing PCI	Death from any causes, MI, or ischemia driven revascularization at 48 h	HR 1.08 (CI 0.80–1.46)	159
DECLARE-DIABETES[a]	400/400	Aspirin + clopidogrel + cilostazol vs aspirin + clopidogrel	Stable angina, UA, MI, or positive stress test and a native coronary lesion	In-stent late loss at 6 months	0.25±0.53 mm vs. 0.38±0.54 mm p=0.025	170
TRA 2P-TIMI 50	6,724/26,449	Vorapaxar vs placebo	History of MI, ischemic stroke, or PAD	Cardiovascular death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization	HR 0.89 (CI 0.78–1.02) $P_{interaction}$=0.61	171
TRACER	4,070/12,944	Vorapaxar vs placebo	ACS	Death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization	HR 0.96 (CI 0.84–1.10) $P_{interaction}$=0.40	172
ATLAS ACS 2-TIMI 51	4,964/15,526	Rivaroxaban vs placebo	ACS	Cardiovascular death, MI, or stroke	HR 0.96 (CI 0.77–1.20) $P_{interaction}$=0.14	174

$P_{interaction}$ values described only if reported in the main trial

ACS acute coronary syndrome, *DM* diabetes mellitus, *HR* hazard ratio, *MI* myocardial infarction, *NSTEMI* non-ST elevation myocardial infarction, *OR* odds ratio, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *RR* relative risk, *RRR* relative risk reduction, *STEMI* ST-elevation myocardial infarction, *TVR* target vessel revascularization, *UA* unstable angina

[a] Indicates studies conducted exclusively in patients with DM; all others are results of DM subgroup analysis

[b] No specific data about patients with DM in the parent CLARITY trial [109]

Conversely, aspirin is the treatment of choice in the secondary prevention of patients with CAD or undergoing PCI [79, 87]. Several studies have broadly demonstrated the efficacy of aspirin in non-ST elevation acute coronary syndromes and ST elevation myocardial infarction (STEMI) and its use is recommended in current guidelines (initial dose of 162–325 mg followed by a daily dose of 75–162 mg) [79, 87, 88]. The use of aspirin for secondary prevention is based on the results of two large meta-analyses involving 212,000 high-risk patients which showed a benefit with oral antiplatelet agents, mainly aspirin (75–325 mg/die), irrespective of DM status. The incidence of vascular events was reduced from 22.3 to 18.5 % in the cohort of DM patients ($p<0.002$), and from 16.4 % to 12.8 % ($p<0.00001$) in non-DM patients [89]. The use of low-dose aspirin (75–150 mg/day) was at least as effective as higher daily doses, while bleeding complications were increased with the higher doses [90].

However, aspirin treatment has some limitations in DM subjects. In fact, several investigations provided correlations between aspirin poor responsiveness and a higher risk of recurrent ischemic events [91, 92]. The prevalence of aspirin resistance varies considerably among studies [93] and the specific mechanisms of aspirin resistance in DM patients have not been entirely elucidated and likely multifactorial. These include hyperglycemia, as augmented protein glycation may be associated with decreased protein acetylation mediated by aspirin [81, 94], increased TXA_2 synthesis [81], and accelerated platelet turnover [94]. Other mechanisms involved in the reduced response to aspirin are type of aspirin used [95], genetic factors [96], drug interactions [97], and low-grade inflammation that may induce an increased TXA_2 synthesis [98].

Clopidogrel

Clopidogrel is a thienopyridine, which is a non-direct, oral antiplatelet agent that irreversibly blocks the platelet ADP $P2Y_{12}$ receptor. $P2Y_1$ and $P2Y_{12}$ receptors mediate the role of ADP on platelets but activation of $P2Y_{12}$ pathway plays the principal role, leading to sustained platelet aggregation and stabilization of the platelet aggregate [99–101]. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial randomized 19,185 high-risk patients (history of recent MI, recent ischemic stroke, or established peripheral artery disease) with atherosclerotic vascular disease to aspirin (325 mg daily) or clopidogrel (75 mg daily) to test their efficacy for secondary prevention [102]. The global results showed that clopidogrel group had a significantly lower annual rate of the composite end-point of ischemic stroke, MI or vascular death (5.32 vs. 5.83 %; $p=0.043$). In particular, the DM sub-group reached a greater benefit with clopidogrel, while the reduction in the rates of ischemic outcomes in patients without DM did not reach statistical significance [103]. The efficacy of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in primary and secondary prevention in patients at high risk for ischemic events, but not presenting with an ACS or undergoing PCI, was evaluated in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial. The results showed that DAPT was not significantly more effective than aspirin alone in reducing the rates of cardiovascular death, MI, or stroke (6.8 vs 7.3 %; $p=0.22$) [104]. Consistent with the results in the overall population, no benefit of combined therapy was observed in the DM subgroup.

Several trials have demonstrated the superiority of DAPT with aspirin and clopidogrel compared to aspirin alone for preventing recurrent ischemic events in patients with ACS and undergoing coronary stenting [105–110] and thus its use is recommended in practice guidelines [79, 88]. Despite the proven efficacy of DAPT with aspirin and clopidogrel, there is a rate (5–40 %) of patients who have recurrent ischemic events while on therapy [111, 112]. These subjects are known as “low responder” or “resistant”. Clopidogrel response variability has been explained by three different mechanisms: genetic, cellular, and clinical factors [113]. Among the clinical mechanisms, DM is considered one of the most important factors both in the acute and maintenance phase of therapy [114, 115]. In fact, platelet ADP $P2Y_{12}$ receptor signaling pathway is upregulated in DM platelets [18, 116], as shown in a mechanistic study in which platelets from patients with DM were hypo-responsive to $P2Y_{12}$ receptor blockade achieved by escalating concentrations of the active metabolite of clopidogrel compared with platelets from non-DM patients [117]. Reduced PD effects in patients treated with thienopyridines may also be attributed to reduced generation of the active metabolites, which has been shown for both clopidogrel and prasugrel [118]. Interestingly, smoking, which is an inducer of CYP1A2 metabolic activity involved in the first oxidation step of clopidogrel metabolism, is associated with enhanced clopidogrel-induced antiplatelet effects and reduced rates of inadequate clopidogrel response in DM patients [119]. Importantly, DM patients with poor metabolic control or at an advanced stage requiring insulin therapy have the worse response to clopidogrel [120]. In addition, DM is a strong risk factor for the development of chronic kidney disease (CKD) which is itself a cause of clopidogrel resistance. A recent analysis performed in 306 DM patients with CAD and on DAPT therapy with aspirin and clopidogrel, showed that the percentage of poor responders to clopidogrel, who also had higher levels of markers of platelet activation, was greatest among patients with moderate to severe CKD [121]. Moreover, the presence of high on-treatment platelet reactivity in DM patients with CAD while on chronic DAPT has

showed to be associated with a higher risk of long-term adverse cardiovascular events [122]. The reduced responsiveness to clopidogrel contributes to explain why DM is also a strong predictor of stent thrombosis [123–125]. Other mechanisms contributing to clopidogrel resistance in DM patients are diminished platelet response to insulin, which leads to increased platelet adhesion, aggregation, and procoagulant activity on contact with collagen [117], dysregulation of calcium metabolism [65], increased exposure to ADP [126], and increased platelet turnover [127].

Novel and Future Strategies of Antiplatelet Therapy in DM Patients

Patients with DM have well-known poor responsiveness to aspirin and clopidogrel with high platelet reactivity and thus greater risk of ischemic events. In this section we will provide insights into three different strategies to optimize platelet inhibition in patients with DM: modification of dosing of commonly used agents (aspirin and clopidogrel), use of new agents and addition of a third antiplatelet drug (triple therapy).

Modification of Aspirin and Clopidogrel Dosing

Increasing the dose of aspirin has been suggested to overcome low responsiveness. A post hoc analysis of the ASPECT (Aspirin-Induced Platelet Effect) study analyzed three aspirin dosages (81, 162, or 325 mg/daily) in DM vs. non-DM patients and showed higher platelet reactivity in the 81-mg DM group compared with non-DM. However, when increasing aspirin dose (162 and 325 mg daily), there was greater platelet inhibition in patients with DM to an extent that the final rates of aspirin resistance were similar between groups [128]. The CURRENT/OASIS-7 (clopidogrel optimal loading dose usage to reduce recurrent events–organization to assess strategies in ischemic syndromes) trial was the first large-scale randomized study comparing high with low-dose aspirin in ACS patients undergoing angiography [129]. Patients were randomized in a 2×2 factorial design to a high or standard dose of clopidogrel for a month and in an open-label fashion to high (300–325 mg daily) versus low dose (75–100 mg daily) aspirin. The trial did not show significant differences in efficacy among aspirin doses with a trend toward an increasing in bleeding. There are no data reported specifically in the DM subset.

The hypothesis that increasing the frequency of aspirin administration (twice daily instead of once daily) has also been advocated as this may result in more effective platelet inhibition based on the fact that the accelerated platelet turnover which characterizes DM subjects may lead to an increased proportion of non-aspirin-inhibited platelets using a daily dosing interval [92, 130]. Several small studies showed a benefit of twice daily aspirin dose on platelet function profiles in DM patients [131–133]. However, it remains unknown if this translates into differences in clinical outcomes.

The recommended loading and maintenance doses for clopidogrel are 300–600 mg and 75 mg/daily, respectively [79, 88]. In the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus) study type 2 DM patients with CAD and high platelet reactivity while in their maintenance phase of clopidogrel therapy were administered high (150 mg) versus standard maintenance dose of clopidogrel (75 mg) and a PD evaluation was performed. The 150-mg dose showed a moderate improvement in platelet inhibition, although approximately 60 % of patients remained with high platelet reactivity [134]. The CURRENT/OASIS-7 trial evaluated also the efficacy of high (600-mg loading dose followed by 150 mg daily for 1 week and then 75 mg/daily until day 30) versus standard dose (300-mg loading followed by 75 mg daily until day 30) of clopidogrel. In the subgroup of patients undergoing PCI the high-dose strategy was associated with a decrease in the rates of ischemic outcomes (3.9 vs. 4.5 %; HR=0.85; p=0.036), and reduced the risk of stent thrombosis by 30 %, at the expense of increased study-defined major bleedings. Consistent findings were observed across subgroups, including according to DM status (p value for interaction=0.872) [135].

The use of a "tailored treatment" in patients with poor clopidogrel response assessed by a platelet function assay has been suggested as a possible strategy. In the GRAVITAS (Gauging Responsiveness with a VerifyNow Assay: Impact on Thrombosis And Safety) trial high-dose clopidogrel (600-mg initial dose and 150 mg daily thereafter for 6 months) in 2,214 patients with high on-treatment reactivity, assessed by the VerifyNow system, 12 to 24 h after PCI with drug-eluting stents, demonstrated no differences in the rates of ischemic (2.3 vs. 2.3 %; HR=1.01; p=0.97) or bleeding outcomes (1.4 vs. 2.3 %; HR=0.59; p=0.10), in comparison to standard therapy [136]. However, there are not specific analyses to the DM cohort of this trial. Recently, the ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting) trial randomized 2,440 patients scheduled for coronary stenting to a strategy of platelet-function monitoring, with drug adjustment in patients who had a poor response to antiplatelet therapy, or to a conventional strategy without monitoring and drug adjustment. In the monitoring group, high platelet reactivity in patients taking clopidogrel (34.5 % of patients) or aspirin (7.6 %) led to the administration of an additional bolus of clopidogrel, prasugrel, or

aspirin along with GP IIb/IIIa inhibitors during the procedure. The trial showed no difference in the primary end-point, a composite of death, MI, stent thrombosis, stroke, or urgent revascularization 1 year after stent implantation, with the monitoring strategy (34.6 vs. 31.1 %; p=0.10) [137]. An interaction analysis showed consistent data across various subgroups including DM (p value for interaction=0.91).

Use of New Agents

Several new antiplatelet agents are currently in different stages of clinical development. Some of these may be considered to tailor the specific dysfunction of DM platelets. For example, DM platelets have a greater production in TXA_2, which may be due to poor metabolic control, increased oxidative stress and increased platelet turnover rates. Thus, inhibition of thromboxane and prostaglandin endoperoxide receptors (TP) may be an interesting therapeutic target [94, 138, 139]. TP inhibitors include picotamide (a combined TXA_2 synthase inhibitor and TP receptor blocker), ridogrel (a combined TXA_2 synthase inhibitor and TP receptor blocker), ramatroban (a TP receptor inhibitor), NCX 4016 (a NO-releasing aspirin derivative), Si8886/terutroban (a TP receptor inhibitor), and EV-077 (a combined TXA_2 synthase inhibitor and TP receptor blocker). These drugs have been evaluated in different clinical settings with variable success and might be of potential interest for future development in DM subjects [140–144].

Prasugrel and ticagrelor are two novel potent $P2Y_{12}$ receptor blockers with important pharmacological advantages over clopidogrel and represent an attractive strategy especially in high-risk patients, such as those with DM. Prasugrel, an oral administered third-generation thienopyridine, is a prodrug which requires hepatic biotransformation into its active metabolite [145]. Compared to clopidogrel, prasugrel has a faster onset of action, greater platelet inhibition due to a more efficient conversion into its active metabolite and less interindividual variability. The OPTIMUS-3 trial showed greater platelet inhibition of prasugrel at standard dose (60-mg loading dose/10-mg maintenance dose) vs. high-dose clopidogrel (600-mg loading dose/150-mg maintenance dose) in type 2 DM patients with CAD on chronic aspirin therapy [146]. Moreover, prasugrel resulted in lower rates of poor responders [146]. The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) examined the efficacy and safety of prasugrel (60-mg loading dose followed by 10 mg daily) versus standard clopidogrel therapy (300-mg loading dose followed by 75-mg/day maintenance dose) in 13,608 patients with moderate- to high-risk ACS undergoing PCI [147]. Prasugrel demonstrated a significant reduction in the rates of the primary end point (composite of cardiovascular death, nonfatal MI, or nonfatal stroke) (9.9 vs. 12.1 %; HR:0.81; p<0.001), as well as a reduction in the rates of stent thrombosis over a follow-up period of 15 months, at the expense of an increased risk of major bleeding. Particular subgroups appeared to have a higher benefit with prasugrel therapy such as patients with STEMI [148], and importantly DM patients [149]. In subjects with DM the primary end point was reduced significantly with prasugrel (12.2 vs. 17.0 %; p<0.001). This benefit was consistent in patients with and without insulin treatment. Of note, major bleeding was higher in DM patients but there were no differences in major bleeding among DM patients treated with prasugrel compared with clopidogrel.

Ticagrelor, a cyclopentyltriazolopyrimidines, is an oral, reversible, non-competitive $P2Y_{12}$ receptor inhibitor with rapid onset and offset of action (requiring twice daily dosing) and provides a stronger and more consistent inhibition of platelet aggregation than clopidogrel [150–153]. The phase III PLATO (Platelet Inhibition and Patient Outcomes) trial randomized ACS patients (n=18,624) to receive either ticagrelor (180-mg loading dose followed by 90 mg twice daily) or clopidogrel (300- to-600-mg loading dose followed by 75 mg daily). Ticagrelor showed a significant reduction in the primary end-point, the combination of death from vascular causes, MI or stroke (9.8 vs. 11.7 %; HR=0.84; p=0.0001), and, remarkably, of cardiovascular death (4.0 vs. 5.1 %; HR=0.79; p=0.001) at 12 months [154]. Moreover, the occurrence of definite or probable stent thrombosis was reduced by ticagrelor treatment in the subgroup of patients undergoing PCI (2.2 vs. 2.9 %; HR=0.75; p=0.02). This higher efficacy was associated with an increased rate of non-coronary artery bypass graft (CABG)-related major bleeding (4.5 vs. 3.8 %; HR=1.19; p=0.03). The predefined subgroup analysis of the DM cohort (n=4,662) showed a numerical but not significant reduction of the rates of the primary end point (14.1 vs. 16.2 %), which was consistent with the overall trial results. The benefit of ticagrelor was enhanced in patients with worse metabolic control, as defined per HbA1c levels above the median (6 %), in which ticagrelor significantly reduced the rates of the primary end point, without difference in major bleeding [155]. Moreover, a new study, the MATTIS-D (Effect of Modifying Anti-platelet Treatment to Ticagrelor in Patients with Diabetes and Low Response to Clopidogrel; NCT01643031), is ongoing to evaluate clinical benefits in patients with diabetes and low response to clopidogrel after switch to ticagrelor.

To date, there are other novel $P2Y_{12}$ inhibitors which are in different stages of development (Table 2). Cangrelor is an intravenous ATP analog with direct-acting and reversible $P2Y_{12}$ receptor inhibitor binding [145, 156]. Cangrelor is characterized by dose-dependent action and can achieve a greater degree of platelet inhibition (>90 %) with extremely

rapid onset and offset of action [157]. Recently, Ferreiro et al. evaluated the in vitro cangrelor PD effects in 103 clopidogrel naïve patients with CAD on aspirin therapy. The authors concluded that in vitro addition of cangrelor provides a potent and dose-dependent blockade of the platelet $P2Y_{12}$ receptor, with no differential effect in patients with and without DM [158]. Despite the promising PD properties of cangrelor, the phase III CHAMPION (cangrelor versus standard therapy to achieve optimal management of platelet inhibition) trials which included CHAMPION-PCI (n=8,716) and CHAMPION-PLATFORM (n=5,362) did not meet the primary endpoint [159, 160], with consistent neutral findings in the DM cohort. A new phase III clinical trial, the CHAMPION-PHOENIX (NCT01156571), is evaluating the efficacy and safety of cangrelor compared to standard of care in patients undergoing PCI.

Elinogrel is another direct-acting new agent which inhibits its $P2Y_{12}$ inhibitor reversibly and can be administered both orally and intravenously [161, 162]. The INNOVATE-PCI (A Randomized, Double-Blind, Active-Controlled Trial to Evaluate Intravenous and Oral PRT060128, a Selective and Reversible P2Y12 Inhibitor, vs Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-Urgent PCI) trial (NCT00751231) has provided promising results of elinogrel in terms of platelet inhibition and safety compared to clopidogrel in patients undergoing non-urgent PCI [163, 164]. There are no specific data with elinogrel in DM subjects and phase III studies with elinogrel are not planned at the current time.

Addition of a Third Antiplatelet Agent

Another strategy that has been advocated to prevent recurrent events despite the use of DAPT with aspirin and clopidogrel, in particular in DM patients, is to add a third agent which blocks pathways other than COX-1 and purinergic $P2Y_{12}$. Drugs that have been suggested to be used on "triple therapy" are: cilostazol, protease-activated receptor-1 (PAR-1) antagonist and novel anticoagulants (Table 2).

Cilostazol is a potent phosphodiesterase (PDE) III inhibitor that increases intraplatelet cyclic adenosine monophosphate concentration and increases platelet inhibition when used with aspirin and clopidogrel [165]. Several investigations, including PD studies specifically conducted in DM patients, confirmed that the addition of cilostazol to standard DAPT is associated with a greater reduction of platelet reactivity, even when compared with clopidogrel 150 mg/daily [166, 167]. The magnitude of these effects appears to be greater in DM patients compared to those without DM, particularly those with high on treatment platelet reactivity [158, 168, 169]. These PD findings may explain the enhanced clinical benefit of adding cilostazol to DAPT in DM patients undergoing PCI [170].

Recently, there has been a broad interest in thrombin receptor antagonists, which block the platelet PAR-1 receptor subtype, including vorapaxar (SCH530348) and atopaxar (E5555) [138]. Vorapaxar has been evaluated in two large phase III clinical trials in CAD patients. The role of vorapaxar in the secondary prevention of patients with known atherosclerotic disease (history of MI, ischemic stroke, or peripheral arterial disease) was recently evaluated in the TRA 2P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events Thrombolysis in Myocardial Infarction 50) trial [171]. In this trial, 26,449 patients were randomized to receive vorapaxar 2.5 mg daily or placebo, in addition to standard of care therapy, including aspirin (94 % of patients) and a thienopyridine (99.3 % clopidogrel). The primary efficacy end-point, a composite of death from cardiovascular causes, MI, or stroke, was significantly reduced in the vorapaxar group at 3 years (9.3 vs. 10.5 %; HR, 0.87; p<0.001). Moderate or severe bleeding occurred in 4.2 % of patients who received vorapaxar and 2.5 % of those who received placebo (HR, 1.66; p<0.001), with an increase in the rate of intracranial hemorrhage in the vorapaxar group (1.0 vs. 0.5 %; p<0.001), especially in patients with a history of stroke. Of note, a composite end point termed net clinical outcome, comprising the primary efficacy and safety end points did not show any significant difference between vorapaxar and placebo (p=0.40). The trial enrolled a total 25 % of DM patients but subgroup analysis showed no difference between DM and non-DM patients in both primary (p value for interaction=0.61) and safety (p value for interaction=0.79) end-points.

The TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial tested whether the addition of vorapaxar to standard therapy would be superior to placebo in reducing recurrent ischemic cardiovascular events in patients with NSTE-ACS [172]. Patients with an ACS within 24 h before hospital admission were randomized to receive vorapaxar (40-mg loading dose and a daily maintenance dose of 2.5 mg) plus standard of care or placebo plus standard of care, including a combination of aspirin (96 % of patients) and a $P2Y_{12}$ inhibitor (clopidogrel in 91.8 % of patients). The TRACER trial, whose follow-up was terminated early after a safety review, showed no significant benefit of vorapaxar in the primary efficacy end-point, a composite of death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization (Kaplan–Meier 2-year rate, 18.5 vs. 19.9 %; HR, 0.92; p=0.07). Vorapaxar significantly decreased the key secondary end point of death from cardiovascular causes, MI or stroke (14.7 vs. 16.4 %; HR, 0.89; p=0.02) but significantly increased the rate of moderate or severe bleeding as compared with placebo (7.2 vs. 5.2 %; HR, 1.35; p<0.001), in particular intracranial

hemorrhage (1.1 vs. 0.2 %; HR, 3.39; $p<0.001$). Primary and key secondary efficacy outcomes were consistent across subgroups. In particular, even in the 31.5 % of patients with DM the addition of vorapaxar to standard therapy did not significantly reduce the primary composite end point (p for interaction=0.4) but significantly increased the risk of major bleeding (p for interaction =0.8), including intracranial hemorrhage.

Triple therapy has also been evaluated with adding novel oral anticoagulants including anti-factor IIa "gatrans" (dabigatran) and direct factor Xa inhibitors or "xabans" (rivaroxaban, apixaban, darexaban) [173]. However, of the various studies only one, using rivaroxaban, completed phase III clinical testing, while others were limited by the high rates of bleeding events. The ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2-Thrombolysis in Myocardial Infarction 51) trial randomized 15,526 ACS patients to rivaroxaban (2.5 or 5 mg bid) or placebo in addition to standard therapy [174]. The primary efficacy outcome (composite cardiovascular death, MI, or stroke) was reduced in the rivaroxaban group with increased of non-CABG related major bleeding and intracranial hemorrhage. Moreover, the reduction in the primary efficacy end point with rivaroxaban was consistent among the subgroups, although the p for interaction for DM cohort (4,964) was not significant (p=0.14).

Conclusions

In conclusion, DM patients are at increased atherothrombotic risk which contributes to their heightened cardiovascular morbidity and mortality. The prothrombotic status, in particular their hyperreactive platelet phenotype, plays a key role in these outcomes. Several mechanisms are involved in the hyperreactive platelet phenotype underscoring the need to define more optimal platelet inhibiting treatment regimens in these patients. The introduction of new antiplatelet agents into the armamentarium of currently available treatment regimens represents a step forward in reaching these objectives. Studies specifically designed in DM assessing the functional and clinical impact of new antithrombotic strategies are warranted to define the optimal treatment for this high-risk group of patients.

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References

1. Inzucchi, S. E. (2012). Diagnosis of diabetes. *The New England Journal of Medicine, 367*, 542–550.
2. Morel, O., Kessler, L., Ohlmann, P., & Bareiss, P. (2010). Diabetes and the platelet: toward new therapeutic paradigms for diabetic atherothrombosis. *Atherosclerosis, 212*, 367–376.
3. Webster MW, Scott RS (1997) What cardiologists need to know about diabetes. Lancet 350 Suppl 1:SI23–8.
4. Haffner, S. M., Lehto, S., Rönnemaa, T., Pyörälä, K., & Laakso, M. (1998). Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *The New England Journal of Medicine, 339*, 229–234.
5. Malmberg, K., Yusuf, S., Gerstein, H. C., Brown, J., Zhao, F., Hunt, D., et al. (2000). Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation, 102*, 1014–1019.
6. Roffi, M., Chew, D. P., Mukherjee, D., Bhatt, D. L., White, J. A., Heeschen, C., et al. (2001). Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation, 104*, 2767–2771.
7. Creager, M. A., Lüscher, T. F., Cosentino, F., & Beckman, J. A. (2003). Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. *Circulation, 108*, 1527–1532.
8. Stratmann, B., & Tschoepe, D. (2005). Pathobiology and cell interactions of platelets in diabetes. *Diabetes & Vascular Disease Research, 2*, 16–23.
9. Angiolillo, D. J., Fernandez-Ortiz, A., Bernardo, E., Ramírez, C., Sabaté, M., Jimenez-Quevedo, P., et al. (2005). Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes, 54*, 2430–2435.
10. Vinik, A. I., Erbas, T., Park, T. S., Nolan, R., & Pittenger, G. L. (2001). Platelet dysfunction in type 2 diabetes. *Diabetes Care, 24*, 1476–1485.

11. Ferroni, P., Basili, S., Falco, A., & Davì, G. (2004). Platelet activation in type 2 diabetes mellitus. *Journal of Thrombosis and Haemostasis, 2*, 1282–1291.
12. Ferreiro, J. L., & Angiolillo, D. J. (2011). Diabetes and antiplatelet therapy in acute coronary syndrome. *Circulation, 123*, 798–813.
13. Geisler, T., Anders, N., Paterok, M., Langer, H., Stellos, K., Lindemann, S., et al. (2007). Platelet response to clopidogrel is attenuated in diabetic patients undergoing coronary stent implantation. *Diabetes Care, 30*, 372–374.
14. Davì, G., & Patrono, C. (2007). Platelet activation and atherothrombosis. *The New England Journal of Medicine, 357*, 2482–2494.
15. Fuster, V., Moreno, P. R., Fayad, Z. A., Corti, R., & Badimon, J. J. (2005). Atherothrombosis and high-risk plaque: part I: evolving concepts. *Journal of the American College of Cardiology, 46*, 937–954.
16. Schneider, D. J. (2009). Factors contributing to increased platelet reactivity in people with diabetes. *Diabetes Care, 32*, 525–527.
17. Lemkes, B. A., Hermanides, J., Devries, J. H., Holleman, F., Meijers, J. C., & Hoekstra, J. B. (2010). Hyperglycaemia, a prothrombotic factor? *Journal of Thrombosis and Haemostasis, 8*, 1663–1669.
18. Ferreiro, J. L., & Angiolillo, D. J. (2012). Challenges and perspectives of antiplatelet therapy in patients with diabetes mellitus and coronary artery disease. *Current Pharmaceutical Design, 1*, 5273–5293.
19. Winocour, P. D., Watala, C., Perry, D. W., & Kinlough-Rathbone, R. L. (1992). Decreased platelet membrane fluidity due to glycation or acetylation of membrane proteins. *Thrombosis and Haemostasis, 68*, 577–582.
20. Watala, C., Golański, J., Boncler, M. A., Pietrucha, T., & Gwoździński, K. (1998). Membrane lipid fluidity of blood platelets: a common denominator that underlies the opposing actions of various agents that affect platelet activation in whole blood. *Platelets, 9*, 315–327.
21. Chappey, O., Dosquet, C., Wautier, M. P., & Wautier, J. L. (1997). Advanced glycation end products, oxidant stress and vascular lesions. *European Journal of Clinical Investigation, 27*, 97–108.
22. Assert, R., Scherk, G., Bumbure, A., Pirags, V., Schatz, H., & Pfeiffer, A. F. (2001). Regulation of protein kinase C by short term hyperglycaemia in human platelets in vivo and in vitro. *Diabetologia, 44*, 188–195.
23. Xia, P., Inoguchi, T., Kern, T. S., Engerman, R. L., Oates, P. J., & King, G. L. (1994). Characterization of the mechanism for the chronic activation of diacylglycerol-protein kinase C pathway in diabetes and hypergalactosemia. *Diabetes, 43*, 1122–1129.
24. Ferretti, G., Rabini, R. A., Bacchetti, T., Vignini, A., Salvolini, E., Ravaglia, F., et al. (2002). Glycated low density lipoproteins modify platelet properties: a compositional and functional study. *Journal of Clinical Endocrinology and Metabolism, 87*, 2180–2184.
25. Williams, S. B., Goldfine, A. B., Timimi, F. K., Ting, H. H., Roddy, M. A., Simonson, D. C., et al. (1998). Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation, 97*, 1695–1701.
26. Nishikawa, T., Edelstein, D., Du, X. L., Yamagishi, S., Matsumura, T., Kaneda, Y., et al. (2000). Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature, 404*, 787–790.
27. Keating, F. K., Sobel, B. E., & Schneider, D. J. (2003). Effects of increased concentrations of glucose on platelet reactivity in healthy subjects and in patients with and without diabetes mellitus. *The American Journal of Cardiology, 92*, 1362–1365.
28. Takada, Y., Urano, T., Watanabe, I., Taminato, A., Yoshimi, T., & Takada, A. (1993). Changes in fibrinolytic parameters in male patients with type 2 (non-insulin-dependent) diabetes mellitus. *Thrombosis Research, 71*, 405–415.
29. Kessler, L., Wiesel, M. L., Attali, P., Mossard, J. M., Cazenave, J. P., & Pinget, M. (1998). Von Willebrand factor in diabetic angiopathy. *Diabetes & Metabolism, 24*, 327–336.
30. Boden, G., & Rao, A. K. (2007). Effects of hyperglycemia and hyperinsulinemia on the tissue factor pathway of blood coagulation. *Current Diabetes Reports, 7*, 223–227.
31. Eibl, N., Krugluger, W., Streit, G., Schrattbauer, K., Hopmeier, P., & Schernthaner, G. (2004). Improved metabolic control decreases platelet activation markers in patients with type-2 diabetes. *European Journal of Clinical Investigation, 34*, 205–209.
32. Vivas, D., García-Rubira, J. C., Bernardo, E., Angiolillo, D. J., Martín, P., Calle-Pascual, A., et al. (2011). Effects of intensive glucose control on platelet reactivity in patients with acute coronary syndromes. Results of the CHIPS Study ("Control de Hiperglucemia y Actividad Plaquetaria en Pacientes con Sindrome Coronario Agudo"). *Heart, 97*, 803–809.
33. Malmberg, K. (1997). Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ, 314*, 1512–1515.
34. Malmberg, K., Rydén, L., Wedel, H., Birkeland, K., Bootsma, A., Dickstein, K., et al. (2005). Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *European Heart Journal, 26*, 650–661.
35. Gerstein, H. C., Miller, M. E., Byington, R. P., Goff, D. C., Jr., Bigger, J. T., Buse, J. B., et al. (2008). Effects of intensive glucose lowering in type 2 diabetes. *The New England Journal of Medicine, 358*, 2545–2559.
36. Finfer, S., Chittock, D. R., Su, S. Y., Blair, D., Foster, D., Dhingra, V., et al. (2009). Intensive versus conventional glucose control in critically ill patients. *The New England Journal of Medicine, 360*, 1283–1297.
37. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care (2010) 33:S62-S69.
38. Hajek, A. S., & Joist, J. H. (1992). Platelet insulin receptor. *Methods in Enzymology, 215*, 398–403.
39. Hunter, R. W., & Hers, I. (2009). Insulin/IGF-1 hybrid receptor expression on human platelets: consequences for the effect of insulin on platelet function. *Journal of Thrombosis and Haemostasis, 7*, 2123–2130.
40. Kahn, N. N. (1998). Insulin-induced expression of prostacyclin receptors on platelets is mediated through ADP-ribosylation of Gi alpha protein. *Life Sciences, 63*, 2031–2038.
41. Randriamboavonjy, V., & Fleming, I. (2009). Insulin, insulin resistance, and platelet signaling in diabetes. *Diabetes Care, 32*, 528–530.
42. Westerbacka, J., Yki-Järvinen, H., Turpeinen, A., Rissanen, A., Vehkavaara, S., Syrjälä, M., et al. (2002). Inhibition of platelet-collagen interaction: an in vivo action of insulin abolished by insulin resistance in obesity. *Arteriosclerosis, Thrombosis, and Vascular Biology, 22*, 167–172.
43. Angiolillo, D. J., Bernardo, E., Zanoni, M., Vivas, D., Capranzano, P., Malerba, G., et al. (2011). Impact of insulin receptor substrate-1 genotypes on platelet reactivity and cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. *Journal of the American College of Cardiology, 58*, 30–39.
44. Ishida, M., Ishida, T., Ono, N., Matsuura, H., Watanabe, M., Kajiyama, G., et al. (1996). Effects of insulin on calcium metabolism and platelet aggregation. *Hypertension, 28*, 209–212.

45. Betteridge, D. J., El Tahir, K. E., Reckless, J. P., & Williams, K. I. (1982). Platelets from diabetic subjects show diminished sensitivity to prostacyclin. *European Journal of Clinical Investigation, 12*, 395–398.
46. Anfossi, G., Mularoni, E. M., Burzacca, S., Ponziani, M. C., Massucco, P., Mattiello, L., et al. (1998). Platelet resistance to nitrates in obesity and obese NIDDM, and normal platelet sensitivity to both insulin and nitrates in lean NIDDM. *Diabetes Care, 21*, 121–126.
47. Russo, I., Traversa, M., Bonomo, K., De Salve, A., Mattiello, L., Del Mese, P., et al. (2010). In central obesity, weight loss restores platelet sensitivity to nitric oxide and prostacyclin. *Obesity (Silver Spring), 18*, 788–797.
48. Randriamboavonjy, V., Pistrosch, F., Bölck, B., Schwinger, R. H., Dixit, M., Badenhoop, K., et al. (2008). Platelet sarcoplasmic endoplasmic reticulum Ca2 + −ATPase and mu-calpain activity are altered in type 2 diabetes mellitus and restored by rosiglitazone. *Circulation, 117*, 52–60.
49. Sidhu, J. S., Cowan, D., Tooze, J. A., & Kaski, J. C. (2004). Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reduces circulating platelet activity in patients without diabetes mellitus who have coronary artery disease. *American Heart Journal, 147*, e25.
50. Nissen, S. E., Nicholls, S. J., Wolski, K., Nesto, R., Kupfer, S., Perez, A., et al. (2008). Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *Journal of the American Medical Association, 299*, 1561–1573.
51. McGuire, D. K., Newby, L. K., Bhapkar, M. V., Moliterno, D. J., Hochman, J. S., Klein, W. W., et al. (2004). Association of diabetes mellitus and glycemic control strategies with clinical outcomes after acute coronary syndromes. *American Heart Journal, 147*, 246–252.
52. Gerstein, H. C., Ratner, R. E., Cannon, C. P., Serruys, P. W., García-García, H. M., van Es, G. A., et al. (2010). Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial. *Circulation, 121*, 1176–1187.
53. Suryadevara, S., Ueno, M., Tello-Montoliu, A., Ferreiro, J. L., Desai, B., Rollini, F., et al. (2012). Effects of pioglitazone on platelet P2Y12-mediated signalling in clopidogrel-treated patients with type 2 diabetes mellitus. *Thrombosis and Haemostasis, 108*, 930–936.
54. Muscari, A., De Pascalis, S., Cenni, A., Ludovico, C., Castaldini, N., Antonelli, S., et al. (2008). Determinants of mean platelet volume (MPV) in an elderly population: relevance of body fat, blood glucose and ischaemic electrocardiographic changes. *Thrombosis and Haemostasis, 99*, 1079–1084.
55. Sugiyama, C., Ishizawa, M., Kajita, K., Morita, H., Uno, Y., Matsubara, K., et al. (2007). Platelet aggregation in obese and diabetic subjects: association with leptin level. *Platelets, 18*, 128–134.
56. Scherrer, U., Nussberger, J., Torriani, S., Waeber, B., Darioli, R., Hofstetter, J. R., et al. (1991). Effect of weight reduction in moderately overweight patients on recorded ambulatory blood pressure and free cytosolic platelet calcium. *Circulation, 83*, 552–558.
57. Anfossi, G., Russo, I., & Trovati, M. (2009). Platelet dysfunction in central obesity. *Nutrition, Metabolism, and Cardiovascular Diseases, 19*, 440–449.
58. Angiolillo, D. J., Fernández-Ortiz, A., Bernardo, E., Barrera Ramírez, C., Sabaté, M., Fernandez, C., et al. (2004). Platelet aggregation according to body mass index in patients undergoing coronary stenting: should clopidogrel loading-dose be weight adjusted? *The Journal of Invasive Cardiology, 16*, 169–174.
59. Sibbing, D., von Beckerath, O., Schömig, A., Kastrati, A., & von Beckerath, N. (2007). Impact of body mass index on platelet aggregation after administration of a high loading dose of 600 mg of clopidogrel before percutaneous coronary intervention. *The American Journal of Cardiology, 100*, 203–205.
60. Hochholzer, W., Trenk, D., Fromm, M. F., Valina, C. M., Stratz, C., Bestehorn, H. P., et al. (2010). Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *Journal of the American College of Cardiology, 55*, 2427–2434.
61. Olufadi, R., & Byrne, C. D. (2006). Effects of VLDL and remnant particles on platelets. *Pathophysiology of Haemostasis and Thrombosis, 35*, 281–291.
62. Pedreño, J., Hurt-Camejo, E., Wiklund, O., Badimón, L., & Masana, L. (2000). Platelet function in patients with familial hypertriglyceridemia: evidence that platelet reactivity is modulated by apolipoprotein E content of very-low-density lipoprotein particles. *Metabolism, 49*, 942–949.
63. Kuhn, F. E., Mohler, E. R., Satler, L. F., Reagan, K., Lu, D. Y., & Rackley, C. E. (1991). Effects of high-density lipoprotein on acetylcholine-induced coronary vasoreactivity. *The American Journal of Cardiology, 68*, 1425–1430.
64. Calkin, A. C., Drew, B. G., Ono, A., Duffy, S. J., Gordon, M. V., Schoenwaelder, S. M., et al. (2009). Reconstituted high-density lipoprotein attenuates platelet function in individuals with type 2 diabetes mellitus by promoting cholesterol efflux. *Circulation, 120*, 2095–2104.
65. Li, Y., Woo, V., & Bose, R. (2001). Platelet hyperactivity and abnormal Ca(2+) homeostasis in diabetes mellitus. *American Journal of Physiology. Heart and Circulatory Physiology, 280*, H1480–489.
66. Mazzanti, L., Rabini, R. A., Faloia, E., Fumelli, P., Bertoli, E., & De Pirro, R. (1990). Altered cellular Ca2+ and Na + transport in diabetes mellitus. *Diabetes, 39*, 850–854.
67. Schaeffer, G., Wascher, T. C., Kostner, G. M., & Graier, W. F. (1999). Alterations in platelet Ca2+ signalling in diabetic patients is due to increased formation of superoxide anions and reduced nitric oxide production. *Diabetologia, 42*, 167–176.
68. Ishii, H., Umeda, F., Hashimoto, T., & Nawata, H. (1991). Increased intracellular calcium mobilization in platelets from patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia, 34*, 332–336.
69. Freedman, J. E. (2008). Oxidative stress and platelets. *Arteriosclerosis, Thrombosis, and Vascular Biology, 28*, s11–16.
70. Seghieri, G., Di Simplicio, P., Anichini, R., Alviggi, L., De Bellis, A., Bennardini, F., et al. (2001). Platelet antioxidant enzymes in insulin-dependent diabetes mellitus. *Clinica Chimica Acta, 309*, 19–23.
71. Jardín, I., Redondo, P. C., Salido, G. M., Pariente, J. A., & Rosado, J. A. (2006). Endogenously generated reactive oxygen species reduce PMCA activity in platelets from patients with non-insulin-dependent diabetes mellitus. *Platelets, 17*, 283–288.
72. Redondo, P. C., Jardin, I., Hernández-Cruz, J. M., Pariente, J. A., Salido, G. M., & Rosado, J. A. (2005). Hydrogen peroxide and peroxynitrite enhance Ca2+ mobilization and aggregation in platelets from type 2 diabetic patients. *Biochemical and Biophysical Research Communications, 333*, 794–802.
73. Ahmed, N. (2005). Advanced glycation endproducts-role in pathology of diabetic complications. *Diabetes Research and Clinical Practice, 67*, 3–21.
74. Hasegawa, Y., Suehiro, A., Higasa, S., Namba, M., & Kakishita, E. (2002). Enhancing effect of advanced glycation end products

on serotonin-induced platelet aggregation in patients with diabetes mellitus. *Thrombosis Research, 107*, 319–323.
75. Schmidt, A. M., Yan, S. D., Wautier, J. L., & Stern, D. (1999). Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. *Circulation Research, 84*, 489–497.
76. Schäfer, A., & Bauersachs, J. (2008). Endothelial dysfunction, impaired endogenous platelet inhibition and platelet activation in diabetes and atherosclerosis. *Current Vascular Pharmacology, 6*, 52–60.
77. Kario, K., Matsuo, T., Kobayashi, H., Matsuo, M., Sakata, T., & Miyata, T. (1995). Activation of tissue factor-induced coagulation and endothelial cell dysfunction in non-insulin-dependent diabetic patients with microalbuminuria. *Arteriosclerosis, Thrombosis, and Vascular Biology, 15*, 1114–1120.
78. Tschoepe, D., Roesen, P., Esser, J., Schwippert, B., Nieuwenhuis, H. K., Kehrel, B., et al. (1991). Large platelets circulate in an activated state in diabetes mellitus. *Seminars in Thrombosis and Hemostasis, 17*, 433–438.
79. Levine, G. N., Bates, E. R., Blankenship, J. C., et al. (2011). American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Journal of the American College of Cardiology, 58*, e44–122.
80. Feit, F., Manoukian, S. V., Ebrahimi, R., Pollack, C. V., Ohman, E. M., Attubato, M. J., et al. (2008). Safety and efficacy of bivalirudin monotherapy in patients with diabetes mellitus and acute coronary syndromes: a report from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *Journal of the American College of Cardiology, 51*, 1645–1652.
81. Davì, G., Catalano, I., Averna, M., Notarbartolo, A., Strano, A., Ciabattoni, G., et al. (1990). Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *The New England Journal of Medicine, 322*, 1769–1774.
82. Investigators, E. T. D. R. S. (1992). Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. *Journal of the American Medical Association, 268*, 1292–300.
83. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh (2008) The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 337:a1840.
84. Ogawa, H., Nakayama, M., Morimoto, T., Uemura, S., Kanauchi, M., Doi, N., et al. (2008). Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *Journal of the American Medical Association, 300*, 2134–141.
85. Rydén, L., Standl, E., Bartnik, M., et al. (2007). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *European Heart Journal, 28*, 88–136.
86. Pignone, M., Alberts, M. J., Colwell, J. A., Cushman, M., Inzucchi, S. E., Mukherjee, D., et al. (2010). Aspirin for primary prevention of cardiovascular events in people with diabetes. *Journal of the American College of Cardiology, 55*, 2878–2886.
87. O'Gara, P. T., Kushner, F. G., Ascheim, D. D., et al. (2013). ACCF/AHA guideline for the management of ST-elevation myocardial infarction. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. doi:10.1016/j.jacc.2012.11.019. 2012.
88. Anderson, J. L., Adams, C. D., Antman, E. M., et al. (2011). ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation, 123*, e426–579.
89. Roux, S., Christeller, S., & Lüdin, E. (1992). Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis: a meta-analysis. *Journal of the American College of Cardiology, 19*, 671–677.
90. Antithrombotic Trialists' Collaboration. (2002). Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ, 324*, 71–86.
91. Snoep, J. D., Hovens, M. M., Eikenboom, J. C., van der Bom, J. G., & Huisman, M. V. (2007). Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. *Archives of Internal Medicine, 167*, 1593–1599.
92. Krasopoulos, G., Brister, S. J., Beattie, W. S., & Buchanan, M. R. (2008). Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis. *BMJ, 336*, 195–198.
93. Grove, E. L., Hvas, A. M., Johnsen, H. L., Hedegaard, S. S., Pedersen, S. B., Mortensen, J., et al. (2010). A comparison of platelet function tests and thromboxane metabolites to evaluate aspirin response in healthy individuals and patients with coronary artery disease. *Thrombosis and Haemostasis, 103*, 1245–1253.
94. Guthikonda, S., Lev, E. I., Patel, R., DeLao, T., Bergeron, A. L., Dong, J. F., et al. (2007). Reticulated platelets and uninhibited COX-1 and COX-2 decrease the antiplatelet effects of aspirin. *Journal of Thrombosis and Haemostasis, 5*, 490–496.
95. Cox, D., Maree, A. O., Dooley, M., Conroy, R., Byrne, M. F., & Fitzgerald, D. J. (2006). Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers. *Stroke, 37*, 2153–2158.
96. Maree, A. O., Curtin, R. J., Chubb, A., Dolan, C., Cox, D., O'Brien, J., et al. (2005). Cyclooxygenase-1 haplotype modulates platelet response to aspirin. *Journal of Thrombosis and Haemostasis, 3*, 2340–2345.
97. Catella-Lawson, F., Reilly, M. P., Kapoor, S. C., Cucchiara, A. J., DeMarco, S., Tournier, B., et al. (2001). Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *The New England Journal of Medicine, 345*, 1809–1817.
98. Cerbone, A. M., Macarone-Palmieri, N., Saldalamacchia, G., Coppola, A., Di Minno, G., & Rivellese, A. A. (2009). Diabetes, vascular complications and antiplatelet therapy: open problems. *Acta Diabetologica, 46*, 253–261.
99. Storey, R. F., Newby, L. J., & Heptinstall, S. (2001). Effects of P2Y(1) and P2Y(12) receptor antagonists on platelet aggregation induced by different agonists in human whole blood. *Platelets, 12*, 443–447.
100. Gachet, C. (2001). ADP receptors of platelets and their inhibition. *Thrombosis and Haemostasis, 86*, 222–232.

101. Turner, N. A., Moake, J. L., & McIntire, L. V. (2001). Blockade of adenosine diphosphate receptors P2Y(12) and P2Y(1) is required to inhibit platelet aggregation in whole blood under flow. *Blood, 98*, 3340–3345.
102. Steering Committee, C. A. P. R. I. E. (1996). A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet, 348*, 1329–1339.
103. Bhatt, D. L., Marso, S. P., Hirsch, A. T., Ringleb, P. A., Hacke, W., & Topol, E. J. (2002). Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *The American Journal of Cardiology, 90*, 625–628.
104. Bhatt, D. L., Fox, K. A., Hacke, W., Berger, P. B., Black, H. R., Boden, W. E., et al. (2006). Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *The New England Journal of Medicine, 354*, 1706–1717.
105. Yusuf, S., Zhao, F., Mehta, S. R., Chrolavicius, S., Tognoni, G., Fox, K. K., et al. (2001). Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *The New England Journal of Medicine, 345*, 494–502.
106. Mehta, S. R., Yusuf, S., Peters, R. J., Bertrand, M. E., Lewis, B. S., Natarajan, M. K., et al. (2001). Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet, 358*, 527–533.
107. Steinhubl, S. R., Berger, P. B., Mann, J. T., 3rd, Fry, E. T., DeLago, A., Wilmer, C., et al. (2002). Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *Journal of the American Medical Association, 288*, 2411–2420.
108. Chen, Z. M., Jiang, L. X., Chen, Y. P., Xie, J. X., Pan, H. C., Peto, R., et al. (2005). Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet, 366*, 1607–1621.
109. Sabatine, M. S., Cannon, C. P., Gibson, C. M., López-Sendón, J. L., Montalescot, G., Theroux, P., et al. (2005). Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *The New England Journal of Medicine, 352*, 1179–1189.
110. Sabatine, M. S., Cannon, C. P., Gibson, C. M., López-Sendón, J. L., Montalescot, G., Theroux, P., et al. (2005). Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *Journal of the American Medical Association, 294*, 1224–1232.
111. Angiolillo, D. J., Fernandez-Ortiz, A., Bernardo, E., Alfonso, F., Macaya, C., Bass, T. A., et al. (2007). Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *Journal of the American College of Cardiology, 49*, 1505–1516.
112. Ferreiro, J. L., & Angiolillo, D. J. (2009). Clopidogrel response variability: current status and future directions. *Thrombosis and Haemostasis, 102*, 7–14.
113. Angiolillo, D. J., & Ferreiro, J. L. (2010). Platelet adenosine diphosphate P2Y12 receptor antagonism: benefits and limitations of current treatment strategies and future directions. *Revista Española de Cardiología, 63*, 60–76.
114. Serebruany, V., Pokov, I., Kuliczkowski, W., Chesebro, J., & Badimon, J. (2008). Baseline platelet activity and response after clopidogrel in 257 diabetics among 822 patients with coronary artery disease. *Thrombosis and Haemostasis, 100*, 76–82.
115. Angiolillo, D. J. (2009). Antiplatelet therapy in diabetes: efficacy and limitations of current treatment strategies and future directions. *Diabetes Care, 32*, 531–40.
116. Matsuno, H., Tokuda, H., Ishisaki, A., Zhou, Y., Kitajima, Y., & Kozawa, O. (2005). P2Y12 receptors play a significant role in the development of platelet microaggregation in patients with diabetes. *Journal of Clinical Endocrinology and Metabolism, 90*, 920–927.
117. Ueno, M., Ferreiro, J. L., Tomasello, S. D., Capodanno, D., Tello-Montoliu, A., Kodali, M., et al. (2011). Functional profile of the platelet P2Y12 receptor signalling pathway in patients with type 2 diabetes mellitus and coronary artery disease. *Thrombosis and Haemostasis, 105*, 730–732.
118. Erlinge, D., Varenhorst, C., Braun, O. O., James, S., Winters, K. J., Jakubowski, J. A., et al. (2008). Patients with poor responsiveness to thienopyridine treatment or with diabetes have lower levels of circulating active metabolite, but their platelets respond normally to active metabolite added ex vivo. *Journal of the American College of Cardiology, 52*, 1968–1977.
119. Ueno, M., Ferreiro, J. L., Desai, B., Tomasello, S. D., Tello-Montoliu, A., Capodanno, D., et al. (2012). Cigarette smoking is associated with a dose–response effect in clopidogrel-treated patients with diabetes mellitus and coronary artery disease: results of a pharmacodynamic study. *JACC. Cardiovascular Interventions, 5*, 293–300.
120. Angiolillo, D. J., Bernardo, E., Ramírez, C., Costa, M. A., Sabaté, M., Jimenez-Quevedo, P., et al. (2006). Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *Journal of the American College of Cardiology, 48*, 298–304.
121. Angiolillo, D. J., Bernardo, E., Capodanno, D., Vivas, D., Sabaté, M., Ferreiro, J. L., et al. (2010). Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease on dual antiplatelet therapy. *Journal of the American College of Cardiology, 55*, 1139–1146.
122. Angiolillo, D. J., Bernardo, E., Sabaté, M., Jimenez-Quevedo, P., Costa, M. A., Palazuelos, J., et al. (2007). Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. *Journal of the American College of Cardiology, 50*, 1541–1547.
123. Iakovou, I., Schmidt, T., Bonizzoni, E., Ge, L., Sangiorgi, G. M., Stankovic, G., et al. (2005). Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *Journal of the American Medical Association, 293*, 2126–2130.
124. Urban, P., Gershlick, A. H., Guagliumi, G., Guyon, P., Lotan, C., Schofer, J., et al. (2006). Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. *Circulation, 113*, 1434–1441.
125. Kuchulakanti, P. K., Chu, W. W., Torguson, R., Ohlmann, P., Rha, S. W., Clavijo, L. C., et al. (2006). Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation, 113*, 1108–1113.
126. Michno, A., Bielarczyk, H., Pawełczyk, T., Jankowska-Kulawy, A., Klimaszewska, J., & Szutowicz, A. (2007). Alterations of adenine nucleotide metabolism and function of blood platelets in patients with diabetes. *Diabetes, 56*, 462–467.
127. Guthikonda, S., Alviar, C. L., Vaduganathan, M., Arikan, M., Tellez, A., DeLao, T., et al. (2008). Role of reticulated platelets and platelet size heterogeneity on platelet activity after dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease. *Journal of the American College of Cardiology, 52*, 743–749.
128. DiChiara, J., Bliden, K. P., Tantry, U. S., Hamed, M. S., Antonino, M. J., Suarez, T. A., et al. (2007). The effect of aspirin dosing on platelet function in diabetic and nondiabetic patients: an analysis from the aspirin-induced platelet effect (ASPECT) study. *Diabetes, 56*, 3014–3019.

129. CURRENT-OASIS 7 Investigators, Mehta, S. R., Bassand, J. P., Chrolavicius, S., Diaz, R., Eikelboom, J. W., et al. (2010). Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *The New England Journal of Medicine, 363*, 930–942.
130. Angiolillo, D. J. (2009). Variability in responsiveness to oral antiplatelet therapy. *The American Journal of Cardiology, 103*(3 Suppl), 27A–34A.
131. Capodanno, D., Patel, A., Dharmashankar, K., Ferreiro, J. L., Ueno, M., Kodali, M., et al. (2011). Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. *Circulation. Cardiovascular Interventions, 4*, 180–187.
132. Rocca, B., Santilli, F., Pitocco, D., Mucci, L., Petrucci, G., Vitacolonna, E., et al. (2012). The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. *Journal of Thrombosis and Haemostasis, 10*, 1220–1230.
133. Di Minno, G., Silver, M. J., Cerbone, A. M., & Murphy, S. (1986). Trial of repeated low-dose aspirin in diabetic angiopathy. *Blood, 68, 886–891.*
134. Angiolillo, D. J., Shoemaker, S. B., Desai, B., Yuan, H., Charlton, R. K., Bernardo, E., et al. (2007). Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. *Circulation, 115*, 708–716.
135. Mehta, S. R., Tanguay, J. F., Eikelboom, J. W., Jolly, S. S., Joyner, C. D., Granger, C. B., et al. (2010). Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet, 376*, 1233–1243.
136. Price, M. J., Berger, P. B., Teirstein, P. S., Tanguay, J. F., Angiolillo, D. J., Spriggs, D., et al. (2011). Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *Journal of the American Medical Association, 305*, 1097–1105.
137. Collet, J. P., Cuisset, T., Rangé, G., Cayla, G., Elhadad, S., Pouillot, C., et al. (2012). Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *The New England Journal of Medicine, 367*, 2100–2109.
138. Angiolillo, D. J., Capodanno, D., & Goto, S. (2010). Platelet thrombin receptor antagonism and atherothrombosis. *European Heart Journal, 31*, 17–28.
139. Mortensen, S. B., Larsen, S. B., Grove, E. L., Kristensen, S. D., & Hvas, A. M. (2010). Reduced platelet response to aspirin in patients with coronary artery disease and type 2 diabetes mellitus. *Thrombosis Research, 126, e318–322.*
140. Fontana, P., Alberts, P., Sakariassen, K. S., Bounameaux, H., Meyer, J. P., & Santana Sorensen, A. (2011). The dual thromboxane receptor antagonist and thromboxane synthase inhibitor EV-077 is a more potent inhibitor of platelet function than aspirin. *Journal of Thrombosis and Haemostasis, 9*, 2109–2111.
141. American Heart Association (1994) Randomized trial of ridogrel, a combined thromboxane A2 synthase inhibitor and thromboxane A2/prostaglandin endoperoxide receptor antagonist, versus aspirin as adjunct to thrombolysis in patients with acute myocardial infarction. The Ridogrel Versus Aspirin Patency Trial (RAPT). Circulation 89:588–595.
142. Gresele, P., Migliacci, R., Procacci, A., De Monte, P., & Bonizzoni, E. (2007). Prevention by NCX 4016, a nitric oxide-donating aspirin, but not by aspirin, of the acute endothelial dysfunction induced by exercise in patients with intermittent claudication. *Thrombosis and Haemostasis, 97*, 444–450.
143. Kariyazono, H., Nakamura, K., Arima, J., Ayukawa, O., Onimaru, S., Masuda, H., et al. (2004). Evaluation of antiplatelet aggregatory effects of aspirin, cilostazol and ramatroban on platelet-rich plasma and whole blood. *Blood Coagulation & Fibrinolysis, 15*, 157–167.
144. Neri Serneri, G. G., Coccheri, S., Marubini, E., & Violi, F. (2004). Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics (DAVID) Study Group. Picotamide, a combined inhibitor of thromboxane A2 synthase and receptor, reduces 2-year mortality in diabetics with peripheral arterial disease: the DAVID study. *European Heart Journal, 25*, 1845–1852.
145. Angiolillo, D. J., & Capranzano, P. (2008). Pharmacology of emerging novel platelet inhibitors. *American Heart Journal, 156*(2 Suppl), S10–15.
146. Angiolillo, D. J., Badimon, J. J., Saucedo, J. F., Frelinger, A. L., Michelson, A. D., Jakubowski, J. A., et al. (2011). A pharmacodynamic comparison of prasugrel vs. high-dose clopidogrel in patients with type 2 diabetes mellitus and coronary artery disease: results of the Optimizing anti-Platelet Therapy In diabetes MellitUS (OPTIMUS)-3 Trial. *European Heart Journal, 32*, 838–846.
147. Wiviott, S. D., Braunwald, E., McCabe, C. H., Montalescot, G., Ruzyllo, W., Gottlieb, S., et al. (2007). Prasugrel versus clopidogrel in patients with acute coronary syndromes. *The New England Journal of Medicine, 357*, 2001–2015.
148. Montalescot, G., Wiviott, S. D., Braunwald, E., Murphy, S. A., Gibson, C. M., McCabe, C. H., et al. (2009). Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet, 373*, 723–731.
149. Wiviott, S. D., Braunwald, E., Angiolillo, D. J., Meisel, S., Dalby, A. J., Verheugt, F. W., et al. (2008). Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation, 118*, 1626–1636.
150. Capodanno, D., Dharmashankar, K., & Angiolillo, D. J. (2010). Mechanism of action and clinical development of ticagrelor, a novel platelet ADP P2Y12 receptor antagonist. *Expert Review of Cardiovascular Therapy, 8*, 151–158.
151. Angiolillo, D. J., & Ueno, M. (2011). Optimizing platelet inhibition in clopidogrel poor metabolizers: therapeutic options and practical considerations. *JACC. Cardiovascular Interventions, 4*, 411–414.
152. Gurbel, P. A., Bliden, K. P., Butler, K., Tantry, U. S., Gesheff, T., Wei, C., et al. (2009). Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation, 120*, 2577–2585.
153. Storey, R. F., Husted, S., Harrington, R. A., Heptinstall, S., Wilcox, R. G., Peters, G., et al. (2007). Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *Journal of the American College of Cardiology, 50*, 1852–1856.
154. Wallentin, L., Becker, R. C., Budaj, A., Cannon, C. P., Emanuelsson, H., Held, C., et al. (2009). Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *The New England Journal of Medicine, 361*, 1–13.
155. James, S., Angiolillo, D. J., Cornel, J. H., Erlinge, D., Husted, S., Kontny, F., et al. (2010). Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. *European Heart Journal, 31*, 3006–3116.

156. Ferreiro, J. L., Ueno, M., & Angiolillo, D. J. (2009). Cangrelor: a review on its mechanism of action and clinical development. *Expert Review of Cardiovascular Therapy, 7*, 1195–1201.
157. Storey, R. F., Wilcox, R. G., & Heptinstall, S. (2002). Comparison of the pharmacodynamic effects of the platelet ADP receptor antagonists clopidogrel and AR-C69931MX in patients with ischaemic heart disease. *Platelets, 13*, 407–413.
158. Ferreiro JL, Ueno M, Tello-Montoliu A, Tomasello SD, Capodanno D, Capranzano P, Dharmashankar K, Darlington A, Desai B, Rollini F, Guzman LA, Bass TA, Angiolillo DJ (2012) Effects of cangrelor in coronary artery disease patients with and without diabetes mellitus: an in vitro pharmacodynamic investigation. *Journal of Thrombosis and Thrombolysis, 35*, 155–164.
159. Harrington, R. A., Stone, G. W., McNulty, S., White, H. D., Lincoff, A. M., Gibson, C. M., et al. (2009). Platelet inhibition with Cangrelor in patients undergoing PCI. *The New England Journal of Medicine, 361*, 2318–2329.
160. Bhatt, D. L., Lincoff, A. M., Gibson, C. M., Stone, G. W., McNulty, S., Montalescot, G., et al. (2009). Intravenous Platelet Blockade with Cangrelor during PCI. *The New England Journal of Medicine, 361*, 2330–2341.
161. Berger, J. S., Roe, M. T., Gibson, C. M., Kilaru, R., Green, C. L., Melton, L., et al. (2009). Safety and feasibility of adjunctive antiplatelet therapy with intravenous elinogrel, a direct-acting and reversible P2Y12 ADP-receptor antagonist, before primary percutaneous intervention in patients with ST-elevation myocardial infarction: the Early Rapid ReversAl of platelet thromboSis with intravenous Elinogrel before PCI to optimize reperfusion in acute Myocardial Infarction (ERASE MI) pilot trial. *American Heart Journal, 158*, 998–1004.
162. Ueno, M., Rao, S. V., & Angiolillo, D. J. (2010). Elinogrel: pharmacological principles, preclinical and early phase clinical testing. *Future Cardiology, 6*, 445–453.
163. Welsh, R. C., Rao, S. V., Zeymer, U., Thompson, V. P., Huber, K., Kochman, J., et al. (2012). A randomized, double-blind, active-controlled phase 2 trial to evaluate a novel selective and reversible intravenous and oral P2Y12 inhibitor elinogrel versus clopidogrel in patients undergoing nonurgent percutaneous coronary intervention: the INNOVATE-PCI trial. *Circulation. Cardiovascular Interventions, 5*, 336–346.
164. Angiolillo, D. J., Welsh, R. C., Trenk, D., Neumann, F. J., Conley, P. B., McClure, M. W., et al. (2012). Pharmacokinetic and pharmacodynamic effects of elinogrel: results of the platelet function substudy from the intravenous and oral administration of elinogrel to evaluate tolerability and efficacy in nonurgent percutaneous coronary intervention patients (INNOVATE-PCI) trial. *Circulation. Cardiovascular Interventions, 5*, 347–356.
165. Angiolillo, D. J., Capranzano, P., Ferreiro, J. L., Ueno, M., Capodanno, D., Dharmashankar, K., et al. (2011). Impact of adjunctive cilostazol therapy on platelet function profiles in patients with and without diabetes mellitus on aspirin and clopidogrel therapy. *Thrombosis and Haemostasis, 106*, 253–262.
166. Jeong, Y. H., Lee, S. W., Choi, B. R., Kim, I. S., Seo, M. K., Kwak, C. H., et al. (2009). Randomized comparison of adjunctive cilostazol versus high maintenance dose clopidogrel in patients with high post-treatment platelet reactivity: results of the ACCEL-RESISTANCE (Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) randomized study. *Journal of the American College of Cardiology, 53*, 1101–1109.
167. Ferreiro, J. L., Ueno, M., Desai, B., Capranzano, P., Capodanno, D., & Angiolillo, D. J. (2012). Impact of adjunctive cilostazol therapy versus high maintenance dose of clopidogrel in suboptimal responders with diabetes mellitus. *Rev Esp Cardiol (Engl)., 65*, 105–106.
168. Capranzano, P., Ferreiro, J. L., Ueno, M., Capodanno, D., Dharmashankar, K., Darlington, A., et al. (2012). Pharmacodynamic effects of adjunctive cilostazol therapy in patients with coronary artery disease on dual antiplatelet therapy: Impact of high on-treatment platelet reactivity and diabetes mellitus status. *Catheterization and Cardiovascular Interventions*. doi:10.1002/ccd.24416.
169. Angiolillo, D. J., Capranzano, P., Goto, S., Aslam, M., Desai, B., Charlton, R. K., et al. (2008). A randomized study assessing the impact of cilostazol on platelet function profiles in patients with diabetes mellitus and coronary artery disease on dual antiplatelet therapy: results of the OPTIMUS-2 study. *European Heart Journal, 29*, 2202–2211.
170. Lee, S. W., Park, S. W., Kim, Y. H., Yun, S. C., Park, D. W., Lee, C. W., et al. (2008). Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus the DECLARE-DIABETES Trial (A Randomized Comparison of Triple Antiplatelet Therapy with Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Diabetic Patients). *Journal of the American College of Cardiology, 51*, 1181–1187.
171. Morrow, D. A., Braunwald, E., Bonaca, M. P., Ameriso, S. F., Dalby, A. J., Fish, M. P., et al. (2012). Vorapaxar in the secondary prevention of atherothrombotic events. *The New England Journal of Medicine, 366*, 1404–413.
172. Tricoci, P., Huang, Z., Held, C., The TRACER Investigators, et al. (2012). Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *The New England Journal of Medicine, 366*, 20–33.
173. De Caterina, R., Husted, S., Wallentin, L., Andreotti, F., Arnesen, H., Bachmann, F., et al. (2012). New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. *Journal of the American College of Cardiology, 59*, 1413–1425.
174. Mega, J. L., Braunwald, E., Wiviott, S. D., Bassand, J. P., Bhatt, D. L., Bode, C., et al. (2012). Rivaroxaban in patients with a recent acute coronary syndrome. *The New England Journal of Medicine, 366*, 9–19.