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REVIEW

Clinical update

Current concepts on coronary revascularization in diabetic patients

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Diabetic mellitus (DM) patients with coronary artery disease (CAD) are at higher risk of cardiovascular events compared with non-DM individuals. While aggressive cardiovascular prevention and adequate blood glucose control remain cornerstones of therapy, the decision when and how to proceed to coronary revascularization in an individual DM patient should be based on the extent of CAD, ischaemic burden, ventricular function, as well as comorbidities. While in patients with stable symptoms, moderate CAD on coronary angiography and preserved left ventricular function a conservative strategy may be a valuable initial strategy, in patients with acute coronary syndromes (ACS) an early invasive approach should be favoured. The revascularization strategy for DM patients with complex multivessel CAD should be discussed within a heart team consisting of cardiologists, cardiac surgeons, and anaesthesiologists. In general, the threshold for coronary artery bypass surgery (CABG) should be lower for DM than for non-DM individuals. In patients undergoing percutaneous coronary intervention, the use of drug-eluting stents (DES) and—in the setting of ACS—of potent platelet inhibitors, such as prasugrel or ticagrelor, should be favoured. In the near future, multiple strategies may further favourably impact the prognosis of DM patients undergoing coronary revascularization. These include alternative antiplatelet agents such as thromboxane receptor inhibitors, the broad use of second generation DES, and possibly the implantation of bioresorbable stents. Coronary artery bypass surgery outcomes may also further improve by wide implementation of arterial revascularization, reduction in perioperative stroke by avoiding clamping of the aorta, reduction in wound infection by minimally invasive techniques, and optimization of post-operative medical management.

Keywords Diabetes mellitus • Acute coronary syndromes • Percutaneous coronary intervention • Coronary artery bypass grafting • Antiplatelet agents • Clopidogrel • Prasugrel • Ticagrelor • Drug-eluting stents

Introduction

Diabetes mellitus (DM) is a metabolic condition characterized by dysfunction in insulin secretion and insulin action resulting in chronic hyperglycaemia and deeply affecting the cardiovascular system. In the last few decades, the prevalence of DM has assumed epidemic proportion in Western countries and is expected to follow a similar pattern in the developing world. It has been estimated that the global prevalence of DM among adults will be 6.4% (285 million individuals) in 2010 and 7.7% (439 million individuals) in 2030.[1] In the USA, the costs related to DM have been estimated at $172 billion in 2007—$116 billion for direct and $58 billion for indirect medical costs such as disability and work loss—while they are expected to rise to $192 billion by 2020.[2]

An example of the deleterious impact of DM on cardiovascular prognosis was illustrated in a Danish population-based study on 3.3 million people showing that DM patients without a history of coronary artery disease (CAD) had the same 5-year cardiovascular mortality as non-DM patients with a history of myocardial infarction (MI).[3] Additional cardiovascular risk factors and comorbidities that negatively impact cardiovascular outcomes are more prevalent in DM patients.[4] However, DM itself is the main cause of accelerated atherogenesis and atherothrombosis observed in this patient population.[5] In Western countries, up to one-fourth of all coronary revascularization procedures—either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)—may involve DM patients. Until recently, comparative data between PCI and CABG in DM were limited to subgroup analyses of randomized trials, while the evidence in favour of myocardial

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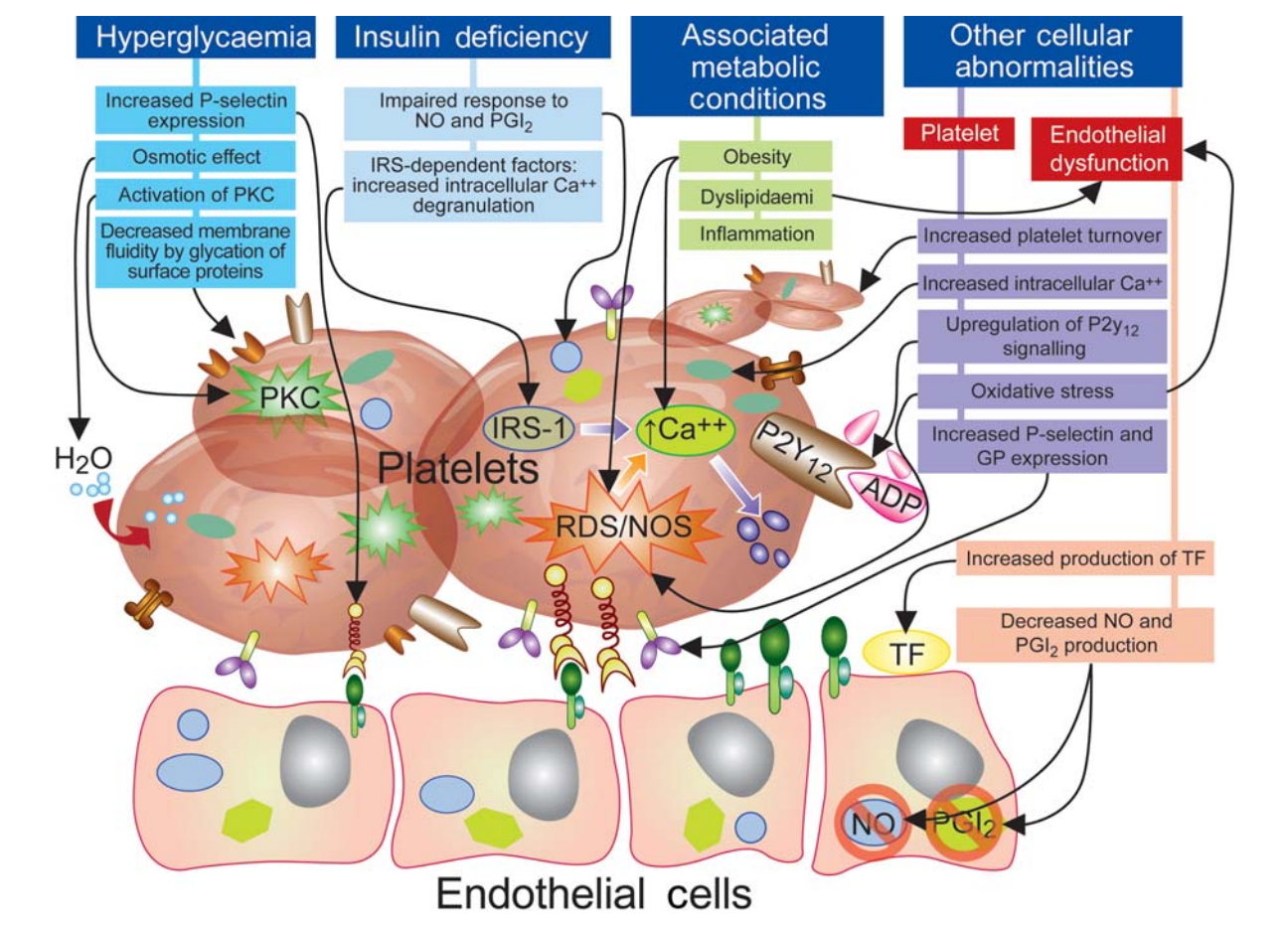

Figure 1 Mechanisms involved in platelet dysfunction and prothrombotic status in diabetes mellitus patients. ADP, adenosine diphosphate; CA^{++}, calcium; GP, glycoprotein; IRS, insulin receptor substrate; NO, nitric oxide; PGI_2, prostacycline; PKC, protein kinase C; ROS/NOS, reactive oxygen and nitrogen species; TF, tissue factor; H_2O, water. Adapted with permission from Ferreiro and Angiolillo.[7]

revascularization over medical management was even sparser. Now, the results of randomized trials including sizable populations of DM patients are available both on myocardial revascularization in stable and unstable patients and on drug-eluting stent (DES)-based PCI vs. CABG in multivessel CAD.

Diabetes-associated atherothrombosis

Prothrombotic and proinflammatory states, in adjunct to endothelial dysfunction and metabolic disorders, such as hyperglycaemia, dyslipidaemia, obesity, insulin resistance, and oxidative stress, are key features of the accelerated atherosclerotic process observed in patients with DM.[5,6] The prothrombotic status is the consequence of multiple conditions, including increased platelet reactivity; increased levels of procoagulant agents such as fibrinogen, tissue factor, von Willebrand factor, platelet factor 4, factor VII; decreased concentrations of endogenous anticoagulants including protein C and antithrombin III; and impaired endogenous fibrinolysis secondary to elevated levels of plasminogen activator inhibitor-1.[7]

As described in *Figure 1*, multiple mechanisms contribute to increased platelet aggregation in DM patients. First, hyperglycaemia may induce the expression of the surface adhesion molecule P-selectin, the glycation of platelet surface proteins with consequent membrane fluidity decrease and platelet adhesion increase, the activation of protein kinase C, and may exert a direct osmotic effect.[7] Hyperglycaemia may also promote atherothrombosis via oxidation of amino groups, formation of advanced glycation end-products, endothelial dysfunction, subendothelial cellular proliferation, and increased matrix expression.[8] Other abnormalities that contribute to the enhanced platelet adhesion and activation in DM include the increased expression of the platelet receptor glycoprotein (GP) IIb/IIIa, up-regulation of platelet $P2Y_{12}$ receptor signalling, increased platelet turnover, and enhanced oxidative stress.[7] Finally, insulin resistance may increase intracellular calcium concentration and impair the response to nitric oxide.

Additional metabolic conditions that may enhance platelet reactivity include obesity (via insulin resistance, augmented cytosolic calcium concentration, and increased oxidative stress), dyslipidaemia, systemic inflammation, and endothelial dysfunction. The latter, a characteristic feature of DM, is mediated by

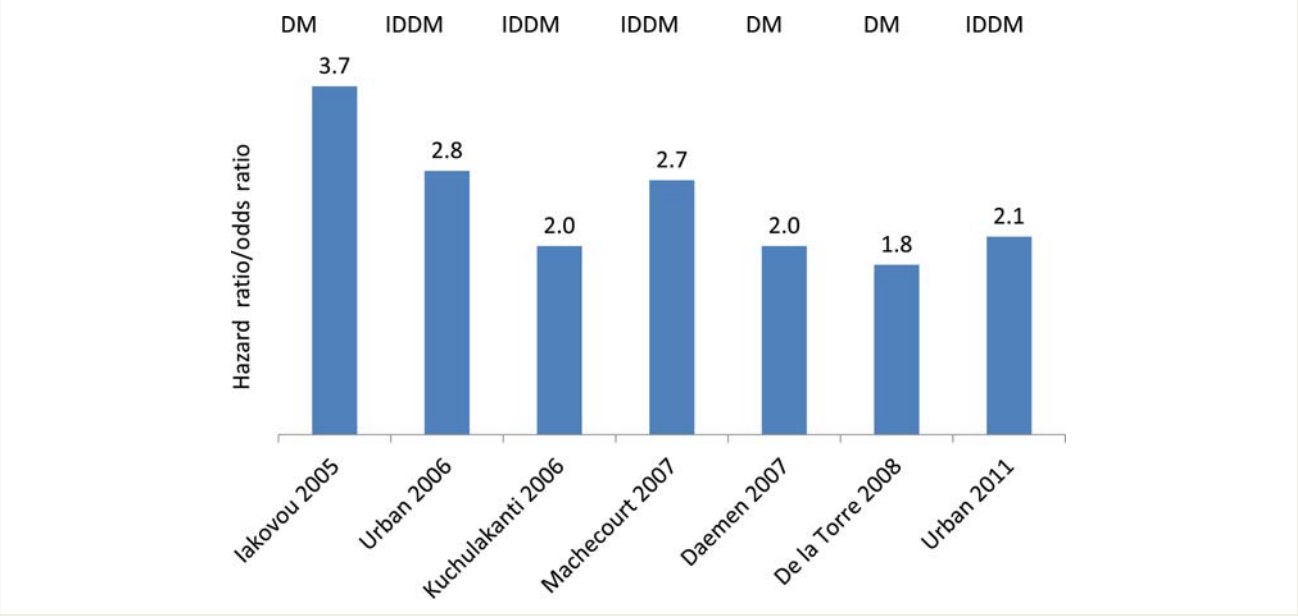

Figure 2 Studies having detected diabetes mellitus or insulin-dependent diabetes mellitus as independent predictor of drug-eluting stent thrombosis. Reported are the hazard ratio or odds ratio of multivariable analyses. Data extracted from Iakovou *et al.*,[65] Urban *et al.*,[66] Kuchulakanti *et al.*,[67] Machecourt *et al.*,[10] Daemen *et al.*,[68] de la Torre *et al.*,[69] and Urban *et al.*[70]

hyperglycaemia, increased free fatty acid production, altered lipoproteins, insulin resistance, and hypertension.[5]

Percutaneous coronary interventions

Impact of drug-eluting stents

The main limitation of bare metal stents (BMS)-based PCI, and more so in DM patients, is restenosis. A meta-analysis of six BMS trials, including 1166 DM and 5070 non-DM patients, detected a restenosis rate of 37% in DM patients and identified DM as an independent predictor of restenosis [odds ratio (OR) 1.3].[9] Even in the DES era, DM patients undergoing PCI have worse outcomes compared with non-DM individuals. The EVASTENT registry enrolled 1731 patients undergoing DES implantation and followed them for a median of 465 days. For each DM patient (stratified as single- or multivessel disease), a non-DM one was subsequently enrolled.[10] The highest major adverse cardiac event (MACE) rate was observed among DM patients with multivessel disease while DM patients with single vessel disease had similar event rates than non-DM individuals with multivessel disease. In addition, DM patients—especially those treated with insulin—had higher mortality as well as stent thrombosis and target vessel revascularization (TVR) rates at 1 year.

Of note, the initial randomized DES investigation in DM patients was troubled by the results of a subgroup analysis of four sirolimus-eluting stents vs. BMS trials including a total of 428 DM patients reporting a statistically significant increase in cardiovascular mortality that persisted at 5 years in patients allocated to DES compared with those treated with BMS.[11] However, subsequent adequately powered studies could not confirm the findings of a harmful effect of DES in DM patients. Accordingly, a network meta-analysis of 35 randomized trials comparing DES with BMS and including 3852 DM patients showed that the use of DES, while not affecting overall mortality or MI rates, was associated with a 60–70% relative risk (RR) reduction in target lesion revascularization (TLR) depending on the type of stent used.[12] As a limitation, the mentioned meta-analysis included trials that differed in terms of patient population enrolled, antiplatelet regimen, and length of follow-up. A beneficial effect of DES in DM was confirmed in large prospective registry of consecutive patients allowing for a comparison of two propensity-matched cohorts of 1476 patients each undergoing DES or BMS implantation.[13] The 3-year risk-adjusted mortality, MI, and TVR rates in the DES vs. BMS propensity matched cohorts were 17.5 vs. 20.7% ($P = 0.02$), 13.8 vs. 16.9% ($P = 0.02$), and 18.4 vs. 23.7% ($P < 0.001$), respectively.

Most of the large-scale clinical investigations showed that the DES thrombosis rate was higher in DM than in non-DM patients and on several occasions DM was identified as independent predictor of stent thrombosis (*Figure* 2). This observation, together with the marked reduction in this complication associated with potent platelet inhibitors such as prasugrel and ticagrelor, supports the notion that the prothrombotic state and the impaired response to dual antiplatelet therapy observed in DM patients are clinically relevant.[14,15]

Differences among drug-eluting stents

In vitro studies have suggested that, due to different signalling pathways, sirolimus may be less effective than paclitaxel in the inhibition of smooth muscle cell migration and survival in an environment

mimicking DM state.[16] However, a meta-analysis of five head-to-head studies dedicated to DM patients ($n = 1173$) demonstrated that the sirolimus-eluting Cypher (Cordis) stent was more effective than the paclitaxel-eluting stent Taxus (Boston Scientific) with respect to TLR (5.1 vs. 11.4%; OR 0.41, $P < 0.001$) and angiographic binary restenosis (5.6 vs. 16.4%; OR 0.30, $P < 0.001$). A subgroup analysis of the DM population ($n = 414$) of the head-to-head trial comparing the biolimus-eluting stent Biomatrix (Biosensor) and the Cypher stent showed no difference in death, MI, or TVR at 9 months.[17] With respect to the everolimus-eluting stent Xience (Abbott), the SPIRIT V registry showed a low rate of death, MI, and TVR at 1 year (6.8%) in 2700 patients and the outcomes of the DM subgroup (30% of the population) did not significantly differ from the overall study results.[18] A head-to-head trial allocating patients to the Xience or the Taxus stent showed low target lesion failure at 1 year in the DM population ($n = 1185$) without differences between the groups (6.4 vs. 6.9%, respectively).[19] Based on current data, none of the DES can be singled out as the device of choice for DM patients.

Coronary artery bypass surgery

In analogy to what observed in PCI, DM negatively affects the outcomes of CABG. A retrospective analysis of the Society of Thoracic Surgery database including 41 663 DM patients among a total population of 146 786 patients showed that the 30-day CABG mortality was significantly increased in DM compared with non-DM individuals (adjusted OR: 1.2).[20] Patients on insulin had the highest mortality rate (adjusted OR: 1.4). In addition, the overall morbidity and the infection rates were significantly elevated in DM patients. Finally, a study on 440 patients undergoing CABG and mandating angiographic follow-up at 1 year identified DM as independent predictor of graft occlusion (RR: 1.45).[21]

A recent randomized study comparing saphenous vein and radial grafting in addition to single internal mammary artery (IMA) bypass suggested that in DM patients ($n = 307$) patency of radial grafts was inferior to saphenous veins, while the opposite was true for non-DM patients ($n = 450$).[22] The Arterial Revascularisation Trial (ART) trial randomized 3102 patients to single vs. bilateral IMA with a primary outcome of survival at 10 years.[23] Mortality at 30 days and 1 year as well as the rates of stroke, MI, and repeat revascularization were similar between the two groups. Sternal wound reconstruction for infection was more frequent in the bilateral IMA group. While no outcome data for the DM subgroup ($n = 734$) are available, it is notable that DM patients suffered half of all sternal wound reconstructions for infection although they accounted for only 24% of the studied population.

At this time it is unknown whether the increased risk of sternal wound infection associated with bilateral IMA grafting in DM patients will be counterbalanced by a long-term benefit.[24] The risk of impaired wound healing may be minimized by avoiding bilateral IMA grafts in obese DM patients and by modification of the IMA dissection technique. Accordingly, IMA 'skeletonization' (i.e. only the IMA is harvested) rather than 'pedicled IMA harvesting' (i.e. the IMA and the surrounding tissue are harvested) may preserve collaterals and sternal blood supply and may improve wound healing, particularly in DM patients.[25] Nevertheless, in a series of 1515 consecutive patients undergoing skeletonized IMA harvesting DM remained an independent predictor of sternal infection (OR: 4.6 and 6.9 for DM patients on oral hypoglycaemic drugs and insulin, respectively).[26]

Percutaneous vs. surgical revascularization

A pooled analysis of individual patient data from 10 randomized trials compared the effectiveness of CABG with angioplasty or BMS-based PCI in 7812 patients with multivessel CAD over a median follow-up of 5.9 years.[27] While among non-DM patients no difference in mortality between CABG and PCI was observed, in patients with DM (CABG, $n = 615$; PCI, $n = 618$), mortality was lower in the surgical group (23%) than in the PCI group (29%) (HR = 0.70, 0.56–0.87) (*Figure 3*).[27] Within a statewide registry, the outcomes of DM patients with multivessel disease treated with CABG ($n = 2844$) did not differ from those undergoing DES-based PCI ($n = 3256$) with respect to the adjusted rate of death (HR = 0.97, $P = 0.75$) and death or MI (HR = 0.84, $P = 0.07$).[28] In the Arterial Revascularization Therapy Study (ARTS)-I study patients were randomized to treatment with a BMS or CABG, whereas in the single-arm ARTS-II study, with similar inclusion criteria, patients underwent DES-based PCI. Among the DM patients included, no difference was observed in terms of mortality or MI between the ARTS-I CABG group ($n = 96$) and the ARTS-II DES group ($n = 159$) but CABG was associated with a lower risk of repeat revascularization (10.7 vs. 33.2%; $P < 0.001$).[29]

The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study randomly assigned 1800 patients (452 with DM) to receive Taxus stents or

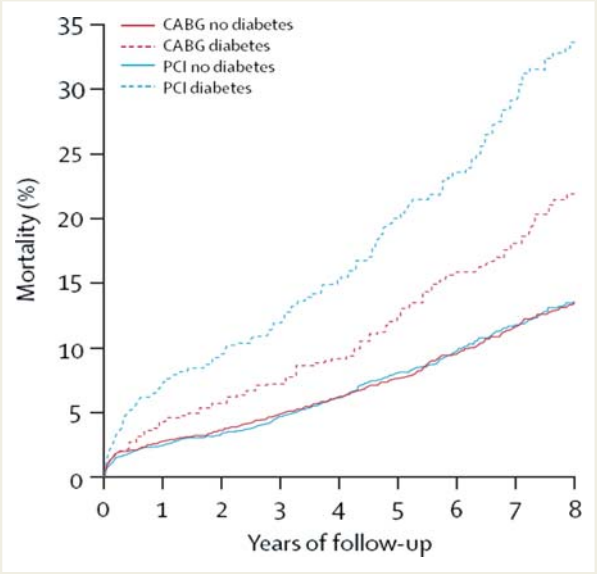

Figure 3 Mortality in patients assigned to coronary artery bypass graft or percutaneous coronary intervention by diabetes status in an analysis of 10 randomized trials. Reproduced with permission from Hlatky *et al.*[27]

Table 1 One-year events in the diabetic subgroup of SYNTAX trial and in the CARDIa trial

	SYNTAX (n = 452)			CARDIa (n = 510)		
	CABG (n = 221) (%)	PCI (n = 231) (%)	P-value	CABG (n = 248) (%)	PCI (n = 254) (%)	P-value
Death	6.4	8.4	0.43	3.2	3.2	0.97
MI	4.4	4.8	0.83	5.7	9.8	0.088
Stroke	2.5	0.9	0.26	2.8	0.4	0.066
Repeat revascularization	6.4	20.3	<0.001	2.0	11.8	<0.001
Death/MI/stroke	10.3	10.1	0.96	10.5	13.0	0.393
Death/MI/stroke repeat revascularization	14.2	26.0	0.003	11.3	19.3	0.016

Data extracted from refs[30,31].
MI, myocardial infarction.

CABG. The pre-specified DM-subgroup analysis showed that, driven by an increased rate of repeat revascularization, the 1-year death, stroke, MI, or repeat revascularization rate was significantly higher among DM patients treated with DES than with CABG while no difference between the groups was observed in the rate of death, stroke, or MI (*Table 1*).[30] The mortality rate was higher after PCI (13.5%) than after CABG (4.1%, $P = 0.04$) in DM patients with highly complex lesions (i.e. SYNTAX score $\geq$33), in those with the lowest SYNTAX score tertile the 1-year death, stroke, MI, or repeat revascularization rate did not differ between CABG and PCI (18.3 vs. 20.3%). These findings suggest that the complexity of CAD rather than DM status should be considered in CABG vs. PCI decision-making. The CARDia (Coronary Artery Revascularization in Diabetes) Trial compared PCI (~1/3 BMS and ~2/3 DES) and CABG in 510 DM patients with multivessel CAD. At 1 year, the primary endpoint of death, MI, and stroke did not differ among the groups while the need of repeat revascularization was significantly higher in the PCI group (*Table 1*).[31]

Overall, CABG should be considered superior to angioplasty or BMS-based PCI in DM patients with multivessel disease both in terms of MACE and late mortality. In the era of first-generation DES, based on the results of the CARDia and SYNTAX trials, it can be stated that at 1-year DM patients treated with PCI or CABG have similar mortality rates as well as a similar rate of the composite of death, MI, or stroke. However, the risk of repeat revascularization remains substantially higher for DM patients undergoing PCI compared with those undergoing CABG. Finally, potential long-term advantages of CABG over PCI include the more complete revascularization and the protection against disease progression in native coronary segments proximal to the anastomosis site.

For the individual DM patient, multiple parameters should be taken into account for the choice of revascularization strategy, such as clinical presentation [acute coronary syndrome (ACS) vs. stable CAD], coronary anatomy, ischaemic burden, previous cardiac surgery, left ventricular function, co-existing comorbidities, and patient preference (*Figure 4*). The recent European myocardial revascularization guidelines recommend revascularization in all stable DM patients with extensive CAD (Class I, level of evidence A).[32] In addition, in DM patients they consider CABG rather than PCI when the extent of the CAD justifies a surgical approach and the patient's risk profile is acceptable (Class IIa, level of evidence B). This consensus document strongly promotes a multidisciplinary approach ('heart team') as the way to guarantee that all therapeutic options (i.e. optimal medical therapy, PCI, and CABG) are transparently discussed.

Medical management vs. revascularization

Stable coronary artery disease

Until recently, little if any data were available on revascularization vs. medical management in DM patients with stable CAD.[33] The Bypass Angioplasty Revascularization Investigation (BARI) 2D trial randomly assigned 2368 DM patients with stable CAD to either prompt revascularization with intensive medical therapy or intensive medical therapy alone.[34] Primary end points were the 5-year rate of death and of MACE defined as a composite of death, MI, or stroke. Randomization was stratified according to the choice of PCI or CABG as the more appropriate intervention. Survival as well as MACE did not differ between the two groups (*Figure 5*). At 5 years, 42% of patients randomized in the conservative arm crossed over to revascularization. With respect to subgroups, while in the PCI stratum there was no significant difference in the primary end points between the revascularization group and the medical therapy group, in the CABG stratum the MACE rate was significantly lower in the revascularization group (22.4%) than in the medical therapy group (30.5%, $P = 0.01$; $P = 0.002$ for interaction between stratum and study group).[34] Importantly, the CABG stratum included patients with a higher risk profile. Therefore, no conclusion should be drawn on the efficacy of PCI vs. CABG based on those results. Overall, the BARI 2D trial shows that in DM patients with stable CAD and no high-risk features on coronary angiography medical therapy may be a valuable initial strategy.

Acute coronary syndromes

Diabetic patients with ACS have worse outcomes than non-DM counterparts. A pooled analysis of several ACS trials including 46 577 STEMI and 15 459 non-ST-ACS patients showed that 30-day

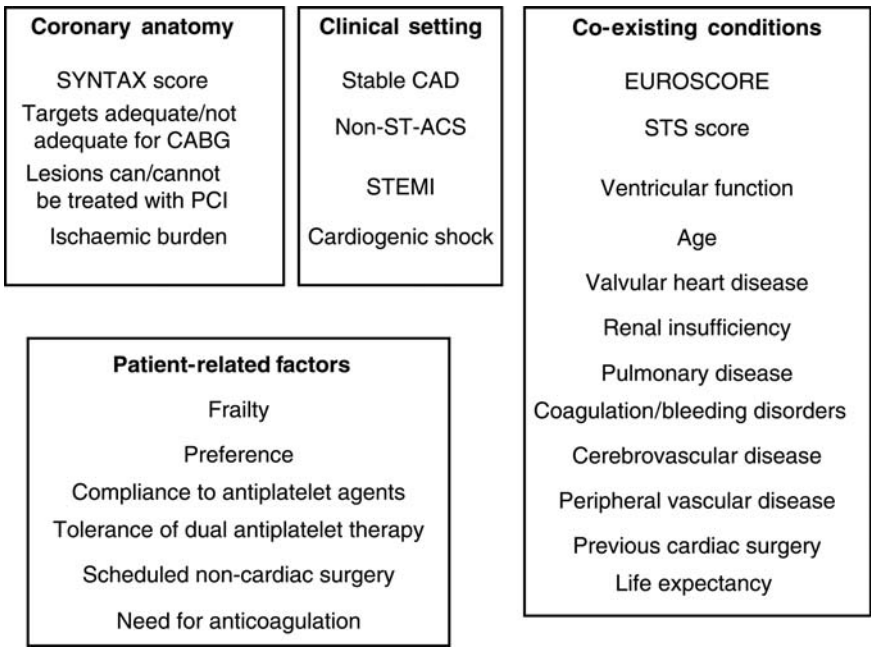

Figure 4 Parameters guiding the choice of revascularization strategy in diabetic patients. STEMI, ST-elevation myocardial infarction; ACS, acute coronary syndromes; CAD, coronary artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary interventions; STS, Society of Thoracic Surgery. Modified with permission from Roffi and Brandle.[71]

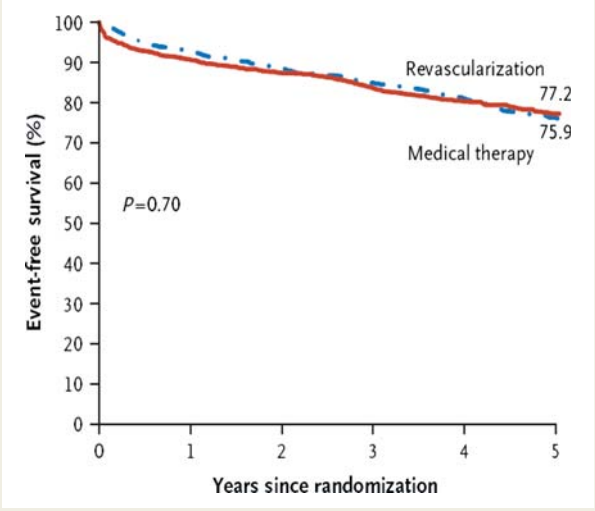

Figure 5 Freedom from major cardiovascular events, revascularization vs. medical therapy at 5 years in the BARI 2D trial. Reproduced with permission from Frye *et al.*[34]

mortality was significantly higher among DM patients both in the setting of non-ST-ACS (2.1 vs. 1.1%, $P < 0.001$) and STEMI (8.5 vs. 5.4%, $P < 0.001$), with an adjusted risk of death of 1.8 and 1.4, respectively.[35] The increased mortality risk persisted at 1 year (HR = 1.7 and 1.2, respectively). Regarding the efficacy of early invasive strategy in non-ST-ACS, the Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) study detected a more pronounced benefit among DM ($n = 299$) than non-DM individuals both in terms of relative (39 vs. 28%) and absolute (9.3 vs. 3.1%) risk reduction for death or MI at 1 year.[36] Similarly, in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial, DM patients ($n = 296$) derived a greater benefit than non-DM individuals from an early invasive strategy both in terms of relative (27% and 13%, respectively) and absolute (7.6 and 1.8%, respectively) reduction in 6-month death, MI, or rehospitalisation for ACS.[37]

The Euro Heart Survey on Diabetes and the Heart recruited 3488 patients (2063 non-DM and 1425 DM) patients with CAD and followed them for 1 year.[38] The population consisted of approximately one-third of stable and two-thirds of unstable CAD patients. While revascularization was of no benefit in non-DM patients, it significantly reduced mortality (5.7 vs. 8.6%) and the rate of death, MI, or stroke (9.9 vs. 16.9%) in DM patients (*Figure 6*). In addition, a statistically significant interaction between DM status and effect of revascularization was observed, suggesting a preferential benefit from revascularization for DM patients.[38] While the American ACS guidelines consider that decision-making with respect to stress testing, angiography, and revascularization should be similar in patients with and without DM, the European ones recommend an early invasive strategy for all DM patients presenting with ACS.[39,40]

Antiplatelet therapy

Numerous investigations have shown that the platelet hyperreactivity observed in DM patients persists under single and dual

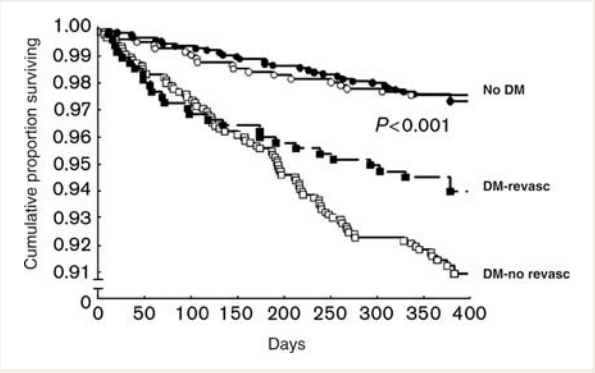

Figure 6 Kaplan–Meier curves on survival comparing patients with and without diabetes who were revascularized or not in the Euro Heart Survey on Diabetes. Reproduced with permission from Anselmino *et al.*[38]

antiplatelet treatments, a phenomenon also coined as 'resistance'.[41,42] The latter may contribute to their higher rates of recurrent atherothrombotic events observed in DM patients with ACS or undergoing PCI. Three classes of antiplatelet agents have been approved for the prevention and treatment of coronary events: aspirin, adenosine diphospate (ADP) $P2Y_{12}$ receptor antagonists, and GP IIb/IIIa inhibitors.

Aspirin

Aspirin selectively and irreversibly acetylates the cycloxigenase-1 (COX-1) enzyme, thereby blocking platelet formation of thromboxane A_2 (TXA_2). In the primary prevention setting, two randomized trials focusing on DM patients were not able to show a benefit from aspirin over placebo.[43,44] The use of low-dose aspirin (75–162 mg/day) for secondary prevention is supported by large meta-analyses, the results of which have been extended to patients with DM.[45] The lack of benefit and the potential for increased bleeding complications of high (300–325 mg) vs. low-dose (75–100 mg) aspirin was recently demonstrated in the CURRENT/OASIS-7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs-Organization to Assess Strategies in Ischemic Syndromes) trial, but no data on DM is available.[46]

Several studies have shown an association between aspirin resistance and a higher risk of recurrent ischaemic events.[47] Aspirin resistance has been described in DM and hyperglycaemia is believed to play an important role in the process via the increased protein glycation with subsequent decrease in aspirin-mediated protein acetylation and reduced sensitivity of platelets to aspirin.[48] In addition, poor DM control and the increased platelet turnover rate described in DM have been associated with an increase in TXA_2 synthesis.[49] Preliminary data suggest that in DM twice daily aspirin regimen, rather than an increase in dose, may be more effective in inhibiting newly generated platelets released into the circulation.[50]

Clopidogrel

The platelet ADP $P2Y_{12}$ receptor plays a central role in platelet activation and aggregation processes. Thienopyridines (i.e.

Table 2 Large-scale randomized placebo-controlled clinical trials evaluating the efficacy of dual antiplatelet therapy with aspirin and clopidogrel vs. aspirin alone in ACS/PCI patients in the overall study population and in diabetes mellitus patients

Study	*n* (overall)	Scenario	Primary endpoint	% of events and association measure (95% CI) in overall population	*n* (diabetes mellitus)	% of events and association measure (95% CI) in DM
CURE	12 562	UA/NSTEMI	Cardiovascular death, non-fatal MI or stroke at 1 year	9.3 vs. 11.4% RR = 0.80 (0.72–0.90)	2840	14.2 vs. 16.7% RR = 0.84 (0.70–1.02)
PCI-CURE	2658	CURE patients undergoing PCI	Cardiovascular death, MI or urgent TVR at 30 days	4.5 vs. 6.4% RR = 0.70 (0.50–0.97)	504	12.9 vs. 16.5% RR = 0.77 (0.48–1.22)
CREDO	2116	Elective PCI	Death, MI or stroke at 1 year	8.5 vs. 11.5% RRR = 26.9% (3.9–44.4%)	560	% NR RRR = 11.2 ((−46.8)–46.2)
COMMIT	45 852	Acute MI (93% STEMI)	Death, reinfarction or stroke at discharge or 28 days	9.2 vs. 10.1% R = 0.91 (0.86–0.97)	NR	NR
CLARITY	3491	STEMI with fibrinolysis	Occluded infarct-related artery on angiography or death or recurrent MI before angiography	15.0 vs. 21.7% OR = 0.64 (0.53–0.76)	575	NR
PCI-CLARITY	1863	CLARITY patients undergoing PCI	Cardiovascular death, recurrent MI, or stroke at 30 days	3.6 vs. 6.2% OR = 0.54 (0.35–0.85)	282 OR = 0.61 (0.24–1.53)	6.0 vs. 10.1%

Adapted with permission from Ferreiro and Angiolillo[7].
CI, confidence interval; DM, diabetes mellitus; MI, myocardial infarction; NR, not reported; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; ACS, acute coronary syndromes; RR, relative risk; RRR, relative risk reduction; STEMI, ST-elevation myocardial infarction; TVR, target vessel revascularization; UA, unstable angina.

ticlopidine, clopidogrel, and prasugrel), are non-direct (i.e. metabolism required), orally administered, and irreversible platelet $P2Y_{12}$ receptor inhibitors. In patients with stable atherosclerotic disease not requiring PCI, dual antiplatelet therapy was of no benefit over aspirin in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, in which 42% ($n = 6555$) of the overall study population had DM.[51] In the setting of ACS/PCI, the recommendation for dual antiplatelet therapy with aspirin and clopidogrel is supported by numerous clinical trials. Of note, despite the higher baseline risk of DM patients, the benefit of dual antiplatelet therapy over aspirin alone was not more pronounced than in the non-DM individuals (*Table* 2). The somehow disappointing efficacy of dual antiplatelet therapy in DM has been attributed to the high on-treatment platelet reactivity ('clopidogrel resistance') observed in DM, especially at its most advanced stage.[42]

The OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus) study evaluated the effect of a 150 vs. 75 mg maintenance dose of clopidogrel in DM patients with high platelet reactivity. The 150 mg maintenance dose was associated with a marked increase in platelet inhibition but a suboptimal clopidogrel response was still present in over half of the patients.[52] In the subgroup of patients undergoing PCI ($n = 17\,232$) of the CURRENT/OASIS-7 trial, a study comparing 600 mg loading dose of clopidogrel followed by 150 mg/day for 6 days and 75 mg/day beyond that to 300 mg loading dose followed by 75 mg/day, high clopidogrel dose regimen significantly reduced ischaemic events as well as the risk of stent thrombosis at 30 days. However, no difference in ischaemic events was observed among DM patients ($n = 3844$) (*Figure* 7).[53]

Prasugrel

Prasugrel, a third-generation thienopyridine, is a prodrug requiring hepatic metabolism to give origin to the active metabolite which irreversibly inhibits the $P2Y_{12}$ receptor.[54] This compound has a more rapid onset of action than clopidogrel and provides greater platelet inhibition due to its more effective conversion into the active metabolite. In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) trial, prasugrel compared with clopidogrel significantly reduced the primary end point of cardiovascular death, MI, or stroke (9.9 vs. 12.1%; HR = 0.81; $P < 0.001$) in patients ($n = 13\,608$) with moderate to high-risk ACS undergoing PCI over a period of 15 months.[55] A significant reduction in the stent thrombosis rate associated with the use of prasugrel was also observed. However, the benefit was hampered by an increased risk of TIMI major non-CABG related bleeding in the prasugrel group (2.4 vs. 1.8%; $P = 0.03$). The reduction in the primary endpoint with prasugrel observed in subjects with DM (12.2 vs. 17.0%; HR = 0.70; $P < 0.001$) was even more pronounced than in non-DM individuals (9.2 vs. 10.6%; HR = 0.86; $P = 0.02$). The benefit was consistent in patients without (11.5 vs. 15.3%; HR = 0.74; $P = 0.009$) and with (14.3 vs. 22.2%; HR = 0.63; $P = 0.009$) insulin treatment.[14] Myocardial infarction was reduced by 18% with prasugrel among subjects without DM (7.2 vs. 8.7%; $P = 0.006$) and by 40% among subjects with DM (8.2 vs. 13.2%; $P < 0.001$). In the interaction analyses for treatment benefit, diabetic status showed a trend ($P = 0.09$) for the primary endpoint and was significant ($P = 0.02$) for MI, suggesting a preferential benefit of prasugrel in the DM population. Importantly, there were no differences in major bleedings among DM patients treated with prasugrel and clopidogrel (2.6 vs. 2.5%). Prasugrel therapy also dramatically reduced stent thrombosis rates compared with clopidogrel in DM patients (overall DM cohort: 2.0 vs. 3.6%; HR = 0.52; $P = 0.007$; insulin-treated patients: 1.8 vs. 5.7%; HR = 0.31; $P = 0.008$).[14] Such enhanced clinical benefit observed in DM patients may be explained by its greater platelet inhibitory effects even compared with double-dose clopidogrel, as shown in the OPTIMUS-3 study.[56]

Ticagrelor

Ticagrelor, a first in class cyclopentyltriazolopyrimidine, is an orally administered, direct-acting (i.e. no metabolism is required) and reversible $P2Y_{12}$ inhibitor with more prompt and potent platelet inhibitory effects than clopidogrel. The PLATO (Platelet Inhibition and Patient Outcomes) trial showed that ticagrelor compared with clopidogrel (300–600 mg) loading significantly reduced the rate of the primary ischaemic endpoint of death from vascular causes, MI or stroke at 12 months (10.2 vs. 12.3%; HR = 0.84; $P = 0.0001$) in ACS patients ($n = 18\,624$) treated either medically or undergoing revascularization (percutaneous or surgical).[57] There was also a reduction in the rate of cardiovascular death (4.0 vs. 5.1%; HR = 0.79; $P = 0.001$) and the occurrence of definite/probable stent thrombosis (2.2 vs. 2.9%; HR = 0.75; $P = 0.02$) in the subgroup of patients undergoing PCI. Importantly, ticagrelor was not associated with an increase on protocol-defined major bleeding (11.6 vs. 11.2%; HR = 1.04; $P = 0.43$), although a higher rate of major bleeding not related to CABG was observed (4.5 vs. 3.8%; HR = 1.19; $P = 0.03$). In a predefined subgroup analysis of the DM cohort ($n = 4662$), the reduction in the primary ischaemic endpoint (HR = 0.88; 95% CI, 0.76–1.03), all-cause mortality (HR = 0.82; 95% CI, 0.66–1.01), and stent thrombosis (HR = 0.65; 95% CI = 0.36–1.17) in the absence of an increase in major bleeding (HR = 0.95; 95% CI = 0.81–1.12) with ticagrelor was consistent with the overall results.[15] A summary of the efficacy of novel strategies to enhance platelet inhibition in DM patients with ACS is reported in *Figure* 7.

Glycoprotein IIb/IIIa inhibitors

Currently, three intravenous GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) are approved for clinical use in the PCI/ACS setting.[58] The introduction of novel antiplatelet treatments described above have led to a reduced utilization of these agents in clinical practice.[59] A meta-analysis of six large randomized ACS trials evaluating the effect of GP IIb/IIIa inhibitors in the absence of systematic clopidogrel use observed a mortality benefit at 30 days in DM patients, particularly those undergoing PCI, associated with the use of these agents.[60] However, the ISAR-SWEET (Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics) trial did not show a benefit of abciximab over placebo on the 1-year risk of death and MI in DM patients undergoing elective PCI after pretreatment with a

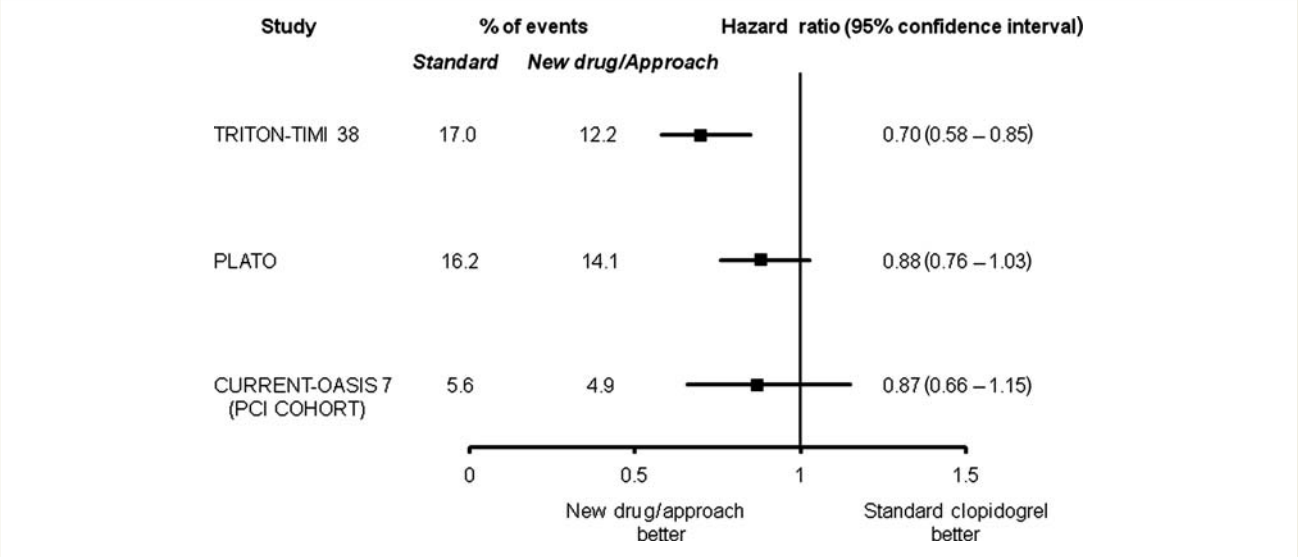

Figure 7 Novel strategies to enhance platelet inhibition in diabetic patients with acute coronary syndromes. The data presented represents the composite of cardiovascular death, myocardial infarction, or stroke in the diabetes mellitus cohorts of TRITON-TIMI 38 (prasugrel vs. clopidogrel), PLATO (ticagrelor vs. clopidogrel), and CURRENT-OASIS 7 (high dose vs. standard dose clopidogrel). Reproduced with permission from Ferreiro and Angiolillo.[7]

600 mg clopidogrel loading dose.[61] Therefore, these results do not support the routine use of GP IIb/IIIa inhibitors in elective PCI in DM patients. On the contrary, the ISAR-REACT 2 (Intracoronary Stenting and Antithrombotic: Regimen Rapid Early Action for Coronary Treatment 2) trial showed a significant reduction in ischaemic events at 30 days with abciximab treatment in patients with high-risk ACS undergoing PCI pretreated with 600 mg of clopidogrel.[62] This benefit, however, was restricted to patients with elevated troponin levels and was observed across all subgroups, including DM patients. These results support the use of GP IIb/IIIa receptor antagonists in high-risk ACS patients undergoing PCI, in particular those with DM. A recent meta-regression analysis of randomized trials showed that GP IIb/IIIa inhibitors in STEMI patients treated with primary PCI to be associated with a benefit in terms of death, but not re-infarction, in high-risk patients, including those with DM.[63] An emerging alternative to the combination of GP IIb/IIIa inhibitors and unfractionated heparin in DM patients with ACS is bivalirudin monotherapy, showing similar ischaemic benefit and reduced bleeding risk.[64]

Future perspectives

Promising antiplatelet strategies include the thromboxane (TP) receptor inhibitors ramatroban and Si8886/terutroban; the combined TXA_2 synthase inhibitors and TP receptor blockers picotamide and ridogrel; and NCX 4016, a NO-releasing aspirin derivative. In addition, several drugs have been suggested to be used as an adjunctive treatment to aspirin and $P2Y_{12}$ inhibitors, leading to the so called 'triple therapy', namely cilostazol; protease-activated receptor-1 antagonists (vorapaxar or SCH530348 and atopaxar or E5555); and new oral anticoagulants including anti-factor IIa (e.g. dabigatran) and anti-factor Xa (e.g. rivaroxaban, apixaban). From a device perspective, there is great hope that bioresorbable stents may be the solution to overcome many if not all limitations of metallic stents. Surgical outcomes may further improve by wide implementation of arterial revascularization, reduction in perioperative stroke by avoiding clamping of the aorta, reduction in wound infection by minimally invasive techniques and optimization of post-operative medical treatment.

Clinical recommendations

While an aggressive cardiovascular prevention strategy and adequate blood glucose control remain cornerstones of the management of DM patients, the decision when and how to proceed to coronary revascularization should be based on multiple parameters including clinical presentation, coronary anatomy, ischaemic burden, left ventricular function, and comorbidities. All DM patients with complex multivessel CAD should be discussed within a heart team, consisting of cardiologists, cardiac surgeons, and anaesthesiologists. Overall, the threshold for CABG should be lower in DM patients than in non-DM individuals. In DM patients undergoing PCI, the use of DES is recommended while in ACS, an early invasive strategy and a broad use of potent platelet inhibitors such as prasugrel and ticagrelor should be favoured.

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References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;**87**:4–14.
2. American Diabetes Association. National Diabetes Fact Sheet, Diabetes Statistics. Available at: http://www.diabetes.org/diabetes-basics/diabetes-statistics/ (2 May 2010).
3. Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, Abildstrom SZ, Hansen ML, Folke F, Buch P, Madsen M, Vaag A, Torp-Pedersen C. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation* 2008;**117**:1945–1954.
4. Roffi M, Topol EJ. Percutaneous coronary intervention in diabetic patients with non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2004;**25**:190–198.
5. Creager MA, Luscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. *Circulation* 2003;**108**:1527–1532.
6. Biondi-Zoccai GG, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. *J Am Coll Cardiol* 2003;**41**:1071–1077.
7. Ferreiro JL, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. *Circulation* 2011;**123**:798–813.
8. Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. *Cardiovasc Res* 1998;**37**:586–600.
9. Gilbert J, Raboud J, Zinman B. Meta-analysis of the effect of diabetes on restenosis rates among patients receiving coronary angioplasty stenting. *Diabetes Care* 2004;**27**:990–994.
10. Machecourt J, Danchin N, Lablanche JM, Fauvel JM, Bonnet JL, Marliere S, Foote A, Quesada JL, Eltchaninoff H, Vanzetto G. Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients: the EVASTENT Matched-Cohort Registry. *J Am Coll Cardiol* 2007;**50**:501–508.
11. Caixeta A, Leon MB, Lansky AJ, Nikolsky E, Aoki J, Moses JW, Schofer J, Morice MC, Schampaert E, Kirtane AJ, Popma JJ, Parise H, Fahy M, Mehran R. 5-year clinical outcomes after sirolimus-eluting stent implantation insights from a patient-level pooled analysis of 4 randomized trials comparing sirolimus-eluting stents with bare-metal stents. *J Am Coll Cardiol* 2009;**54**:894–902.
12. Stettler C, Allemann S, Wandel S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, De Carlo M, Erglis A, Chechi T, Ortolani P, Schalij MJ, Diem P, Meier B, Windecker S, Juni P. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 2008;**337**:a1331.
13. Garg P, Normand SL, Silbaugh TS, Wolf RE, Zelevinsky K, Lovett A, Varma MR, Zhou Z, Mauri L. Drug-eluting or bare-metal stenting in patients with diabetes mellitus: results from the Massachusetts Data Analysis Center Registry. *Circulation* 2008;**118**:2277–2285.
14. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, Verheugt FW, Goodman SG, Corbalan R, Purdy DA, Murphy SA, McCabe CH, Antman EM. 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* 2008;**118**:1626–1636.
15. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, Maya J, Nicolau JC, Spinar J, Storey RF, Stevens SR, Wallentin L. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J* 2010;**31**:3006–3016.
16. Patterson C, Mapera S, Li HH, Madamanchi N, Hilliard E, Lineberger R, Herrmann R, Charles P. Comparative effects of paclitaxel and rapamycin on smooth muscle migration and survival: role of AKT-dependent signaling. *Arterioscler Thromb Vasc Biol* 2006;**26**:1473–1480.
17. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008;**372**:1163–1173.
18. Grube E, Chevalier B, Smits P, Dzavik V, Patel TM, Mullasari AS, Wohrle J, Stuteville M, Dorange C, Kaul U. The SPIRIT V study: a clinical evaluation of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions. *JACC Cardiovasc Interv* 2011;**4**:168–175.
19. Kereiakes DJ, Cutlip DE, Applegate RJ, Wang J, Yaqub M, Sood P, Su X, Su G, Farhat N, Rizvi A, Simonton CA, Sudhir K, Stone GW. Outcomes in diabetic and nondiabetic patients treated with everolimus- or paclitaxel-eluting stents: results from the SPIRIT IV clinical trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System). *J Am Coll Cardiol* 2011;**56**:2084–2089.
20. Carson JL, Scholz PM, Chen AY, Peterson ED, Gold J, Schneider SH. Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. *J Am Coll Cardiol* 2002;**40**:418–423.
21. Desai ND, Naylor CD, Kiss A, Cohen EA, Feder-Elituv R, Miwa S, Radhakrishnan S, Dubbin J, Schwartz L, Fremes SE. Impact of patient and target-vessel characteristics on arterial and venous bypass graft patency: insight from a randomized trial. *Circulation* 2007;**115**:684–691.
22. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Fremes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih MC, Lee K. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA* 2011;**305**:167–174.
23. Taggart DP, Altman DG, Gray AM, Lees B, Nugara F, Yu LM, Campbell H, Flather M. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). *Eur Heart J* 2010;**31**:2470–2481.
24. Kappetein AP. Bilateral mammary artery vs. single mammary artery grafting: promising early results: but will the match finish with enough players? *Eur Heart J* 2010;**31**:2444–2446.
25. Matsa M, Paz Y, Gurevitch J, Shapira I, Kramer A, Pevny D, Mohr R. Bilateral skeletonized internal thoracic artery grafts in patients with diabetes mellitus. *J Thorac Cardiovasc Surg* 2001;**121**:668–674.
26. Pevni D, Uretzky G, Mohr A, Braunstein R, Kramer A, Paz Y, Shapira I, Mohr R. Routine use of bilateral skeletonized internal thoracic artery grafting: long-term results. *Circulation* 2008;**118**:705–712.
27. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrie D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kahler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009;**373**:1190–1197.
28. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med* 2008;**358**:331–341.
29. Onuma Y, Wykrzykowska JJ, Garg S, Vranckx P, Serruys PW. 5-Year follow-up of coronary revascularization in diabetic patients with multivessel coronary artery disease: insights from ARTS (arterial revascularization therapy study)-II and ARTS-I trials. *JACC Cardiovasc Interv* 2011;**4**:317–323.
30. Banning AP, Westaby S, Morice MC, Kappetein AP, Mohr FW, Berti S, Glauber M, Kellett MA, Kramer RS, Leadley K, Dawkins KD, Serruys PW. Diabetic and non-diabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. *J Am Coll Cardiol* 2010;**55**:1067–1075.
31. Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, de Belder M, Baumbach A, Angelini G, de Belder A, Oldroyd KG, Flather M, Roughton M, Nihoyannopoulos P, Bagger JP, Morgan K, Beatt KJ. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol* 2010;**55**:432–440.
32. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: The Task Force on

Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010;**31**:2501–2555.
33. Soares PR, Hueb WA, Lemos PA, Lopes N, Martinez EE, Cesar LA, Oliveira SA, Ramires JA. Coronary revascularization (surgical or percutaneous) decreases mortality after the first year in diabetic subjects but not in nondiabetic subjects with multivessel disease: an analysis from the Medicine, Angioplasty, or Surgery Study (MASS II). *Circulation* 2006;**114**:I420–I424.
34. Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;**360**:2503–2515.
35. Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, Antman EM. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007;**298**:765–775.
36. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. *Lancet* 2000;**356**:9–16.
37. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**:1879–1887.
38. Anselmino M, Malmberg K, Ohrvik J, Ryden L. Evidence-based medication and revascularization: powerful tools in the management of patients with diabetes and coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. *Eur J Cardiovasc Prev Rehabil* 2008;**15**:216–223.
39. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Kristensen SD, Widimsky P, McGregor K, Sechtem U, Tendera M, Hellemans I, Gomez JL, Silber S, Funck-Brentano C, Andreotti F, Benzer W, Bertrand M, Betriu A, DeSutter J, Falk V, Ortiz AF, Gitt A, Hasin Y, Huber K, Kornowski R, Lopez-Sendon J, Morais J, Nordrehaug JE, Steg PG, Thygesen K, Tubaro M, Turpie AG, Verheugt F, Windecker S. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. *Eur Heart J* 2007;**28**:1598–1660.
40. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr. 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* 2011;**123**:e426–e579.
41. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P, Hernandez R, Moreno R, Escaned J, Alfonso F, Banuelos C, Costa MA, Bass TA, Macaya C. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes* 2005;**54**:2430–2435.
42. Angiolillo DJ, Bernardo E, Ramirez C, Costa MA, Sabate M, Jimenez-Quevedo P, Hernandez R, Moreno R, Escaned J, Alfonso F, Banuelos C, Bass TA, Macaya C, Fernandez-Ortiz A. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *J Am Coll Cardiol* 2006;**48**:298–304.
43. 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. 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* 2008;**337**:a1840.
44. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;**300**:2134–2141.
45. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
46. Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, Granger CB, Jolly S, Joyner CD, Rupprecht HJ, Widimsky P, Afzal R, Pogue J, Yusuf S. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010;**363**:930–942.
47. Snoep JD, Hovens MM, Eikenboom JC, van der Bom JG, Huisman MV. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. *Arch Intern Med* 2007;**167**:1593–1599.
48. Watala C, Pluta J, Golanski J, Rozalski M, Czyz M, Trojanowski Z, Drzewoski J. Increased protein glycation in diabetes mellitus is associated with decreased aspirin-mediated protein acetylation and reduced sensitivity of blood platelets to aspirin. *J Mol Med* 2005;**83**:148–158.
49. Davi G, Catalano I, Averna M, Notarbartolo A, Strano A, Ciabattoni G, Patrono C. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *N Engl J Med* 1990;**322**:1769–1774.
50. Capodanno D, Patel A, Dharmashankar K, Ferreiro JL, Ueno M, Kodali M, Tomasello SD, Capranzano P, Seecheran N, Darlington A, Tello-Montoliu A, Desai B, Bass TA, Angiolillo DJ. Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. *Circ Cardiovasc Interv* 2011;**4**:180–187.
51. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;**354**:1706–1717.
52. Angiolillo DJ, Shoemaker SB, Desai B, Yuan H, Charlton RK, Bernardo E, Zenni MM, Guzman LA, Bass TA, Costa MA. 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* 2007;**115**:708–716.
53. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, Faxon DP, Rupprecht HJ, Budaj A, Avezum A, Widimsky P, Steg PG, Bassand JP, Montalescot G, Macaya C, Di Pasquale G, Niemela K, Ajani AE, White HD, Chrolavicius S, Gao P, Fox KA, Yusuf S. 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* 2010;**376**:1233–1243.
54. Angiolillo DJ, Suryadevara S, Capranzano P, Bass TA. Prasugrel: a novel platelet ADP P2Y12 receptor antagonist. A review on its mechanism of action and clinical development. *Expert Opin Pharmacother* 2008;**9**:2893–2900.
55. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.
56. Angiolillo DJ, Badimon JJ, Saucedo JF, Frelinger AL, Michelson AD, Jakubowski JA, Zhu B, Ojeh CK, Baker BA, Effron MB. 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. *Eur Heart J* 2011;32:838–846.
57. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
58. Roffi M, Chew D, Mukherjee D, Bhatt D, White J, Moliterno D, Heeschen C, Hamm C, Robbins M, Kleiman N, Theroux P, White H, Topol E. Platelet glycoprotein IIb/IIIa inhibition in acute coronary syndromes. Gradient of benefit related to the revascularization strategy. *Eur Heart J* 2002;**23**:1441–1448.
59. Roffi M, Mukherjee D. Platelet glycoprotein IIb/IIIa receptor inhibitors—end of an era? *Eur Heart J* 2008;**29**:429–431.
60. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C, Hamm CW, Moliterno DJ, Califf RM, White HD, Kleiman NS, Theroux P, Topol EJ. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation* 2001;**104**:2767–2771.
61. Mehilli J, Kastrati A, Schuhlen H, Dibra A, Dotzer F, von Beckerath N, Bollwein H, Pache J, Dirschinger J, Berger PP, Schomig A. Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 2004;**110**:3627–3635.
62. Kastrati A, Mehilli J, Neumann FJ, Dotzer F, ten Berg J, Bollwein H, Graf I, Ibrahim M, Pache J, Seyfarth M, Schuhlen H, Dirschinger J, Berger PB, Schomig A. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 2006;**295**:1531–1538.
63. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. *Eur Heart J* 2009;**30**:2705–2713.

64. Feit F, Manoukian SV, Ebrahimi R, Pollack CV, Ohman EM, Attubato MJ, Mehran R, Stone GW. 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. *J Am Coll Cardiol* 2008;**51**:1645–1652.
65. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**:2126–2130.
66. Urban P, Gershlick AH, Guagliumi G, Guyon P, Lotan C, Schofer J, Seth A, Sousa JE, Wijns W, Berge C, Deme M, Stoll HP. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. *Circulation* 2006;**113**:1434–1441.
67. Kuchulakanti PK, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, Kim SW, Bui A, Gevorkian N, Xue Z, Smith K, Fournadjieva J, Suddath WO, Satler LF, Pichard AD, Kent KM, Waksman R. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation* 2006;**113**:1108–1113.
68. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007;**369**:667–678.
69. de la Torre-Hernandez JM, Alfonso F, Hernandez F, Elizaga J, Sanmartin M, Pinar E, Lozano I, Vazquez JM, Botas J, Perez de Prado A, Hernandez JM, Sanchis J, Nodar JM, Gomez-Jaume A, Larman M, Diarte JA, Rodriguez-Collado J, Rumoroso JR, Lopez-Minguez JR, Mauri J. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos). *J Am Coll Cardiol* 2008;**51**:986–990.
70. Urban P, Abizaid A, Banning A, Bartorelli AL, Baux AC, Dzavik V, Ellis S, Gao R, Holmes D, Jeong MH, Legrand V, Neumann FJ, Nyakern M, Spaulding C, Worthley S. Stent thrombosis and bleeding complications after implantation of sirolimus-eluting coronary stents in an unselected worldwide population: a report from the e-SELECT (Multi-Center Post-Market Surveillance) registry. *J Am Coll Cardiol* 2011;**57**:1445–1454.
71. Roffi M, Brandle M. Diabetes. In Topol EJ, Teirstein PS eds. *Textbook of Interventional Cardiology*. 6th ed. Philadelphia, PA, USA: Elsevier; 2011, in print.