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# Impact of diabetes on acute coronary syndrome management

## Summary

Diabetic patients with non-ST-segment elevation acute coronary syndromes (ACS) are at greater risk of subsequent cardiovascular events compared with nondiabetic counterparts. However, at the same time they derive greater benefit from aggressive antithrombotic therapy, early coronary angiography, and stent-based percutaneous coronary intervention. State-of-the-art antithrombotic therapy for diabetic patients with ACS include aspirin, clopidogrel, platelet glycoprotein IIb/IIIa receptor antagonists, and heparin or low-molecular-weight heparin. Both in the diabetic and nondiabetic population, drug-eluting stents lead to a dramatic reduction in restenosis. This exceptional therapeutic efficacy is expected to significantly improve the prognosis of diabetic patients with ACS.

*Key words: diabetes and acute coronary syndrome; antithrombotic therapy; stent-based percutaneous coronary intervention; drug-eluting stents*

## Zusammenfassung

Diabetische Patienten mit akutem Koronarsyndrom (AKS) ohne ST-Hebungen im EKG weisen ein erhöhtes kardiovaskuläres Risiko verglichen mit Nicht-Diabetikern auf. Gleichzeitig profitieren sie aber mehr von einer aggressiven antithrombotischen Therapie, einer frühen invasiven Abklärung und, falls indiziert, einer perkutanen koronaren Intervention. Die optimale antithrombotische Therapie des diabetischen Patienten mit AKS beinhaltet Aspirin, Clopidogrel, ein Glykoprotein-IIb/IIIa-Rezeptorantagonist und Heparin oder niedermolekulares Heparin. Sowohl bei Nicht-Diabetikern als auch bei Diabetikern haben die medikamentös beschichteten Stents eine dramatische Senkung der Restenose zur Folge. Diese aussergewöhnliche Therapiewirksamkeit wird weiter die Pro-

gnose des diabetischen Patienten mit AKS verbessern.

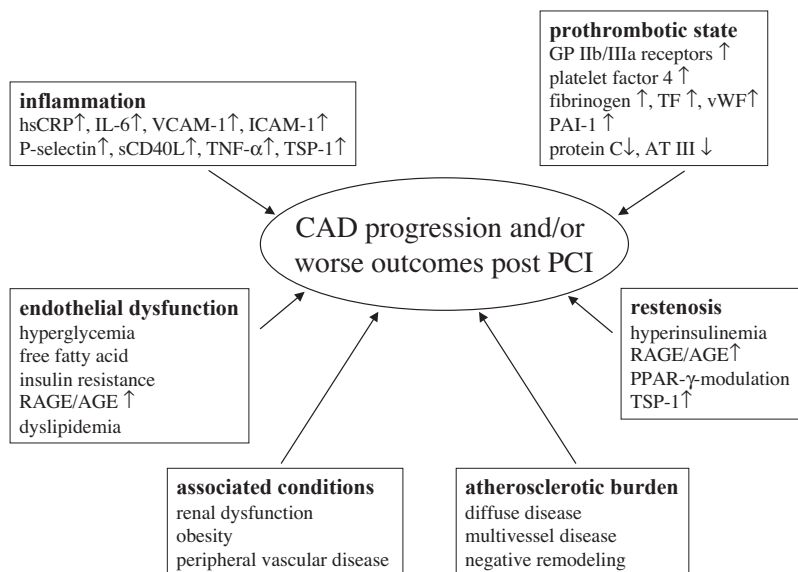
*Key words: Diabetes mellitus und akutes Koronarsyndrom; antithrombotische Therapie; perkutane koronare Intervention; medikamentös beschichtete Stents*

## Introduction

It is estimated that sixteen million people in the US have diabetes mellitus, a condition that may shorten life expectancy by up to 15 years. Atherosclerosis accounts for about 80% of all deaths, of which roughly three-quarters are attributable to coronary artery disease and the remainder to cerebrovascular or peripheral vascular events. As the prevalence of diabetes is estimated to double by the year 2025, the burden of cardiovascular disease associated with this condition will dramatically increase. Of particular concern is the observation that, although over the last two decades cardiovascular mortality has considerably declined, the diabetes-related mortality has increased [1]. The interaction between diabetes and coronary disease is complex, particularly in the acute setting, and a detailed approach of putative underlying mechanisms is beyond the scopes of this review [2]. Pathologic and angiographic studies support the notion that diabetic patients have more diffuse and advanced coronary artery disease than non-diabetics. In addition to coronary disease, diabetic cardiovascular involvement is characterised by higher prevalence of hypertension, heart

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**Figure 1**  
 Pathophysiology of coronary artery disease (CAD) progression and potential factors negatively affecting outcomes following percutaneous coronary intervention (PCI) among diabetic patients. hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; VCAM-1 = vascular cell adhesion molecule-1; ICAM-1 = intracellular adhesion molecule-1; sCD40L = soluble CD40 ligand; TNF- $\alpha$  = tumor necrosis factor  $\alpha$ ; TSP-1 = thrombospondin-1; RAGE = receptor for advanced glycation end-products (AGE); GP = glycoprotein; TF = tissue factor; vWF = von Willebrand factor; PAI-1 = plasminogen activator inhibitor-1; AT = antithrombin; PPAR- $\gamma$  = peroxisome proliferator-activated receptor  $\gamma$ .  
 Reproduced from Roffi M, Topol EJ [2].

failure, peripheral vascular and cerebrovascular disease, and nephropathy (fig. 1).

On top of that several biological and metabolic abnormalities may confer vulnerability to diabetic individuals for cardiovascular events and potentially influence the outcomes following revascularisation. Of particular interest in the setting of acute coronary syndromes (ACS) is the finding that diabetic patients are characterised by both a prothrombotic and an inflammatory state (fig. 1) [3]. The interaction between the diabetes and inflammation appears particularly complex. Although it is plausible that metabolic disturbances associated with this condition trigger vascular inflammation, the converse may also be true. Accordingly, CRP was shown to independently predict the risk of later developing type 2 diabetes [4]. For the purpose of this review the term ACS will refer exclusively to non-ST-segment elevation acute coronary syndromes.

### Outcome of diabetic patients with acute coronary syndromes

Diabetic patients have worse outcomes in the setting of ST-segment elevation acute myocardial infarction. Accordingly, an analysis of the fibrinolytic trial GUSTO-1 involving over

41 000 patients demonstrated that diabetic individuals had higher short-term (ie, 30-day) and mid-term (ie, 1-year) mortality compared with non-diabetics [5]. We recently demonstrated that the same is true for non-ST-elevation ACS. Accordingly, in a retrospective pooled analysis almost 25 000 patients, diabetic patients had almost doubled 30-day mortality compared with non-diabetic counterparts (5.5% vs 3.0%;  $p < 0.001$ ) [6]. In addition, diabetes was found to be an independent predictor of mortality (hazard ratio 1.7).

### Percutaneous coronary intervention

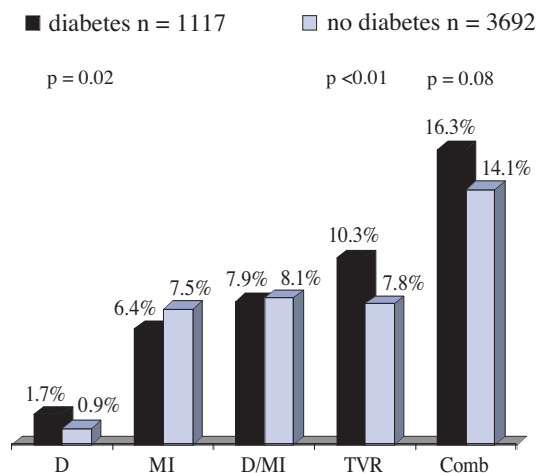
Since state-of-the-art management of ACS include an early invasive strategy consisting of coronary angiography and if appropriate coronary revascularisation, it is worthy to spend few words in describing current results of percutaneous coronary intervention (PCI) among diabetic patients. While in-hospital and 30-day outcomes after PCI have been generally comparable to those of non-diabetics, large-scale registries have frequently shown diabetes to be an independent predictor of long-term mortality and need for repeat revascularisation [7]. Underlying mechanisms that may be related to this inferior outcome include endothelial dysfunction, prothrombotic state, greater propensity for restenosis and negative vascular remodeling, increased protein glycosylation and vascular matrix deposition. These mechanisms appear to be potentiated by hyperglycaemia and hyperinsulinaemia [2].

Although, the placement of intracoronary stent reduces the incidence of restenosis, the rate among diabetic patients remain well above that of non-diabetics. Nevertheless, in the TARGET trial we demonstrated that modern PCI, based on stenting and administration of multiple antiplatelet agents (aspirin, clopidogrel, and a glycoprotein IIb/IIIa receptor inhibitor), substantially improved outcomes in this high-risk patient population [8]. When compared with non-diabetic patients ( $n = 3692$ ), those with diabetes ( $n = 1117$ ) had similar 30-day event rates. In addition, no difference in major adverse cardiac events at 6 months was observed among the two groups, though a trend favoured non-diabetics (fig. 2). Overall, the results of this trial indicate that in patients with suitable coronary anatomy, stent-based PCI with triple antiplatelet therapy performs well even in diabetic patients.



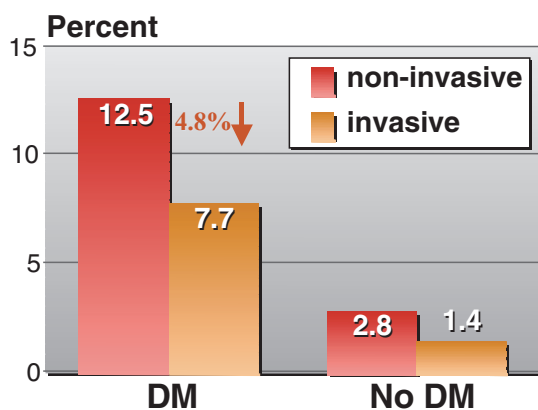
**Figure 2**

Outcomes at 6 months in the TARGET trial according to diabetes status. D = death; MI = myocardial infarction; TVR = target vessel revascularisation; Comb = combined endpoint. Reproduced from Roffi M et al. [8].



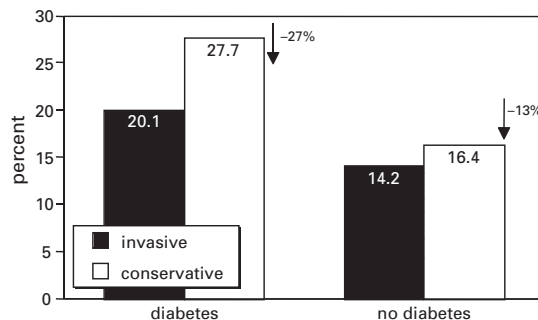
**Figure 3**

1-year mortality in the FRISC II trial according to diabetes status. DM = diabetes mellitus. Reproduced from Wallentin et al. [14].



**Figure 4**

6-month event rates (death, myocardial infarction or rehospitalisation for acute coronary syndromes) in the TACTICS trial according to diabetes status. Reproduced from Cannon et al. [15].



extraordinary reduction in restenosis previously reported in the RAVEL trial [11]. Among diabetic patients enrolled in the SIRIUS trial (n = 279), the sirolimus-eluting stent was associated with dramatic reduction in restenosis compared with the bare stent (6.9% vs 22.3%; p < 0.001). The relative risk reduction for restenosis was of the same magnitude among diabetic and non-diabetic patients (70–80%). Due to higher event rates, the absolute benefit derived within the diabetic population was greater than among non-diabetics. Similar impressive results have been recently presented also with taxol-eluting stents in the TAXUS IV trial [12]. Despite these striking findings, several observations suggest that diabetic restenosis may be particularly resilient to therapy. Accordingly, in the SIRIUS trial diabetes remained an independent predictor of poor angiographic and clinical outcome among patients undergoing eluting stent implantation.

**Early invasive versus conservative strategy**

In diabetic patients with non-ST-segment elevation ACS, the positive impact of an early invasive strategy can be derived from subgroup analyses of large-scale randomised studies. The FRISC II study randomised around 2500 patients with ACS to an invasive or conservative strategy [13]. Allocation to the invasive strategy was associated with a significant 22% reduction in death or myocardial infarction (MI) at 6 months. Among diabetic patients, the invasive strategy was associated with a similar reduction in the relative risk of death or MI and, due to higher events rates, a greater reduction in the absolute risk (6.2%) compared with non-diabetics (2.3%). At one year, diabetic patients undergoing early invasive therapy had a 38% reduction in the relative risk of death (7.7% vs 12.5%), albeit not reaching statistical significance due to the small sample size (n = 299) (fig. 3) [14].

In the TACTICS trial, an early (ie, within 48 hours) invasive strategy was associated with a significant 22% reduction in the relative risk of death, MI, or rehospitalisation for ACS at 6 months compared with an early conservative strategy among 2220 patients [15]. All patients were treated with aspirin, clopidogrel and the glycoprotein IIb/IIIa receptor inhibitor tirofiban. Diabetic patients derived a greater benefit than non-diabetics from an early invasive strategy both in terms of absolute (7.6% and 1.8%, respectively) and relative 6-months event reduction (27% and 13%,

**Restenosis and drug eluting stents**

Restenosis in diabetic patients is characterised by heightened proliferative response and increased vascular matrix deposition. Specific mechanisms that may play a role in this setting have been described elsewhere [2]. Similarly to patients without diabetes, diabetic individuals derive a tremendous benefit from drug-eluting stents. Drug-eluting stents are highly sophisticated device consisting of three components, namely the stent, the polymer, and the drug [9]. The SIRIUS trial [10] randomised 1101 patients to the sirolimus-eluting or bare metal stent and confirmed the

respectively) (fig. 4). Therefore, an early invasive assessment and if appropriate revascularisation should be considered the strategy of choice for diabetic patients with ACS.

### Adjunctive pharmacologic treatment

The efficacy some of the most important pharmacologic players in ACS is summarised with particular attention to the diabetic population. Additional detail on the antithrombotic therapy in ACS can be found elsewhere [16].

#### Clopidogrel

Clopidogrel inhibit platelets by blocking the ADP receptor. Therefore, aspirin and ADP antagonists may have an additive effect in terms of both efficacy and bleeding complications. The CURE trial randomised patients with ACS primarily medically managed to aspirin or aspirin and clopidogrel. Diabetic patients (n = 2840) derived only a modest benefit from the combined treatment for 3 to 12 months (death, MI, or stroke rate 14.2% versus 16.7%; p = ns). Among patients undergoing PCI the benefit of the combined antiplatelet therapy was somehow less marked (relative risk [RR] 0.77) among diabetic patients compared with non-diabetics (RR 0.66) [17]. The CREDO study randomised patients undergoing PCI to a loading dose of clopidogrel followed by 12-month therapy or no loading dose and clopidogrel treatment for 1 month. Among 560 diabetic patients, the benefit of pre-treatment/prolonged clopidogrel therapy was modest (relative risk reduction [RRR] 11%) compared to the one observed among 1556 non-diabetics (RRR 33%)

[18]. Therefore, clopidogrel treatment does not to appear to be associated with a preferential benefit among diabetic patients, as observed with glycoprotein IIb/IIIa receptor inhibitors as described below. Nevertheless, clopidogrel should be administered in addition to aspirin to all diabetic patients with ACS unless contraindicated.

#### Glycoprotein IIb/IIIa receptor antagonists

The glycoprotein (GP) IIb/IIIa receptor is the platelet binding site for fibrinogen. Occupancy of the receptor leads to blockage of fibrinogen cross-linking among platelets and consequent profound inhibition of platelet aggregation. Large-scale randomised clinical trials have established the efficacy of GP IIb/IIIa receptor antagonists in PCI, demonstrating a reduction in periprocedural myocardial infarctions and improved long-term survival[19]. In the EPI-STENT trial, the GP IIb/IIIa antagonist abciximab halved the risk of death, MI, or urgent revascularisation at 30 days among stented patients with diabetes (from 12.1% to 5.6%). The event rate was comparable to that of abciximab treated non-diabetic patients (5.2%) [20]. A pooled analysis of the early abciximab trials demonstrated a survival benefit at 1 year among diabetic patients receiving the GP IIb/IIIa inhibitor compared with placebo (mortality 4.5% vs 2.5%; p = 0.031) at 1 year [21].

While we showed that the overall impact of GP IIb/IIIa receptor inhibitors in the medical management of non-ST-segment elevation ACS has been modest [22], we detected a mortality benefit among diabetic patients. In a meta-analysis of the diabetic populations (n >6400) enrolled in the six large-scale platelet glycoprotein IIb/IIIa inhibitor ACS trials we documented a 26% mortality reduction associated with the use of these agents at 30 days compared with placebo, from 6.2% to 4.6% (p = 0.007) (fig. 5) [23]. These findings were reinforced by a statistically significant interaction between treatment and diabetic status. Even more striking was the benefit among diabetic patients undergoing PCI, with a 70% 30-day mortality reduction, from 4.0% to 1.2% (p = 0.002). Further studies are needed to define whether the preferential benefit observed among diabetics may be related to diabetes-associated conditions such as increased platelet activation, heightened inflammation, or more diffuse atherosclerosis with a propensity for microvascular embolisation. Even without the elucidation of the mechanism, the data are compelling enough that the use of GP IIb/IIIa

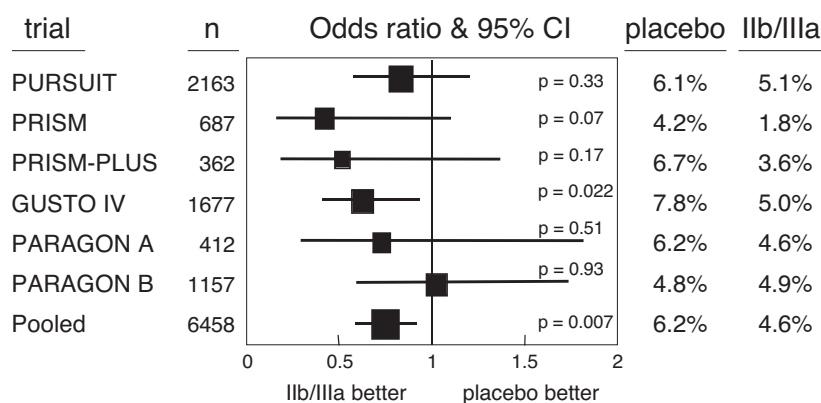


Figure 5

Odds ratio with 95% confidence intervals (CI) and corresponding p-values for treatment effect on 30-day mortality among diabetic patients with acute coronary syndromes. Values to left of 1.0 indicate a survival benefit of platelet glycoprotein IIb/IIIa inhibition (IIb/IIIa). Reproduced from Roffi et al. [23].

inhibitors should be considered standard of care for all diabetic patients presenting with ACS.

### Conclusions

Diabetic patients with ACS are at high risk for subsequent cardiovascular events but derive at the same time greater benefit from aggressive therapy than the non-diabetic counterparts. The mainstays of therapy include potent antiplatelet therapy (ie, aspirin, clopidogrel, and GP IIb/IIIa receptor antagonists), heparin or LMWH, early invasive assessment and, if appropriate, stent-based PCI. CABG may be an alternative in patients with complex coronary anatomy. However, surgeons are frequently reluctant to operate in the setting of ongoing ischaemia. The use of drug-eluting stents is associated with a dramatic reduction in restenosis both among non-diabetic and diabetic individuals. Therefore, a further improvement in the outcomes of diabetic patients with ACS is to be expected.

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