Review Article

Prognosis and Management of Diabetic Patients with Acute Coronary Syndrome

Evangelos G. Pissimissis, Stefanos E. Garoufalis

Cardiology Department, Tzaneio General Hospital of Piraeus

Key words:
Acute coronary syndrome, diabetes mellitus, angioplasty, stents, coronary bypass surgery, platelet GP IIb/IIIa inhibitors.

Manuscript received:
January 15, 2004;
Accepted:
August 18, 2004.

Address:
E.G. Pissimissis

Zefyrou 43,
166 73 Voula, Greece
e-mail:
episimisis@teledomenet.gr

Diabetes mellitus (DM), especially type 2, is a very significant risk factor for coronary artery atherosclerosis, which mainly manifests itself as cardiovascular disease and is accompanied by serious complications (renovascular hypertension, left ventricular diastolic dysfunction, platelet disorders, etc.).

Cardiovascular complications are more common among diabetic patients and are usually associated with a significantly higher risk of morbidity and mortality than in non-diabetic patients.[1,2] The risk for a diabetic is the same as that for a non-diabetic with a previous infarction, as far as the probability of the occurrence of an infarction is concerned.

Consequently, the diabetic patient needs special management and monitoring, with a view to the prevention, control and treatment of the various manifestations of vascular disease. This applies particularly in the case of ischemic heart disease, since the patient should be considered, at the level of cardiovascular risk modification, as a patient with coronary artery disease (CAD).

A recent angiographic study involving 466 patients, of which 34% had unstable angina with no history of prior infarction, showed that diabetics have diffuse and extensive coronary artery atherosclerosis, a higher incidence of slight, moderate and severe stenoses, as well as double the number of complete occlusions as do non-diabetic patients.[3] An important finding is that patients with mild DM (blood glucose 126-140 mg/dl) have the same lesion morphology and atherosclerotic profile as those with normal glucose levels. However, they have more lesions with <50% stenosis. This difference probably explains the greater morbidity and increased cardiac mortality seen in this subgroup, on account of the fact that these small lesions are more susceptible to rupture, which can cause acute coronary syndrome (ACS). Of course, it should be noted that, while 2/3 of acute coronary syndromes are related with angiographically moderate stenoses, the probability of a given stenosis being implicated in an acute syndrome is in proportion to its severity. This makes it imperative and essential to employ a special cardiovascular and metabolic approach to these patients. As a metabolic disease, DM, apart from its clinical manifestations, is characterized by biological aberrations that have specific significance.

The importance of effective control of hyperglycemia

It has been shown that prolonged hyperglycemia, while a less strong prognostic factor than LDL cholesterol, age, sex and systemic hypertension, leads in the long term to significantly more severe coronary artery atheromatosis. An increase in blood glucose levels (>140 mg% in a fasting state) plays a decisive role in the pathogenesis of CAD. Hyperglycemia slows endothelium-dependent vasodilation and acts negatively on lipids and clotting factors. Chronic hyperglycemia glycosylates the proteins and damages the vessels of the kidneys, causing secondary hypertension. It also has a toxic action on the vascular wall, accelerating atheromatosis.[4] So far, cardiologists around the world not have not accorded hyperglycemia the same significance they give to other risk factors for CAD. It appears, however, that the effective control of blood glucose levels can play an important role in reducing the complications and improving the long-term outcome in diabetic patients.

The DIGAMI study,[5] in the context of secondary prevention, investigated 620 diabetic patients with acute myocardial infarction and showed, over a 3.5 year follow up, that aggressive management, with insulin administration, can achieve a material reduction in mortality (8.6% versus 18.0%) compared with dietary treatment or the classical treatment with anti-diabetic tablets. The beneficial action of insulin is probably due to an improvement in metabolic deviation, control of catecholamine levels in the blood and ischemic myocardium, and contributes to a reduction in free fatty acids. Several subsequent studies[6,7] confirmed the findings of DIGAMI.

Additionally, significant differences have been found between the various anti-diabetic drugs, and this fact should be borne seriously in mind by cardiologists. It has been maintained that in ACS glimepiride (sulfonylurea), in contrast to glybenclamide, does not have an inhibitory effect on the appearance of ischemic preconditioning, which is known to contribute to a reduction in infarct size,[8] although this was not confirmed by the large British UKPDS study.

The latter study followed patients with type 2 diabetes over a period of 10 years, during which they were taking either anti-diabetic tablets or insulin, and compared them with those receiving conventional treatment. Patients taking insulin had 12% less risk for each endpoint related to DM, a marginally significant reduction in the incidence of acute infarction, but no significant decrease (6%). In contrast, no differences were observed in the subgroup who were taking anti-diabetic tablets.

The UKPDS study and other clinical-interventional studies, such as DCCT,[10] have shown that reducing levels of glucose to below 150 mg/dl, or glycosylated hemoglobin [HbA1c] by 7%, not only leads to a material reduction in the microvascular complications of diabetic retinopathy, renal function and kidney disease, but also contributes to a reduction in cardiovascular complications and major events. Furthermore, it was recently reported[11] that the simultaneous strict regulation of LDL cholesterol to levels <100 mg/dl resulted in a 50% reduction of major cardiovascular events (non-fatal infarction, death, surgical reperfusion or new percutaneous procedure) over a 12-month follow up.

In view of the above, vigilance and a greater sensitivity are needed with regard to the strict imposition of health and dietary rules and the administration of active and effective anti-diabetic medication aimed at maintaining low levels of blood glucose while controlling hyperlipidemia, especially in patients with proven CAD.

Diabetes mellitus and invasive procedures

CAD is implicated in 75% of all deaths of diabetics, while around 20-25% of patients with unstable angina and myocardial infarction without ST elevation (NSTEMI) are diabetic. Among patients with unstable angina and NSTEMI, diabetics exhibit more severe CAD, with a significantly greater incidence of ulcerated atheromatous plaques (94% versus 60%) and intracoronary thrombi (94% versus 55%) than non-diabetics. Furthermore, CAD is accompanied by an increase in the cohesion of the platelets, which are usually of greater size and bear a larger number of GP IIb/IIIa receptors. Diabetics also show compromised fibrinolysis and coronary reserve with concomitant disturbances of the microcirculation.

As a result of all these biological abnormalities, diabetic patients with CAD suffer more major events after conventional angioplasty (PTCA) and are more likely to need further target vessel revascularization.[12]

However, is coronary artery bypass surgery (CABG) a reliable alternative solution? In 1997 the findings were published from the BARI clinical trial,[13] which compared CABG with PTCA in patients with multi-vessel disease (64% had unstable angina) and showed, in a series of diabetics who participated in the study, that those who underwent CABG had a lower 5-year mortality than those randomized to PTCA (5.8% versus 20.6%).

The beneficial effect of surgical reperfusion, in terms of mortality, was limited to the subgroup of patients in whom the internal mammary artery was grafted. Another important finding was that CABG in diabetic patients, compared with PTCA, was correlated with a reduction in mortality at the next myocardial infarction, whereas no difference was found in non-diabetics.[14] Moreover, the need for further target vessel revascularization was greater in diabetics randomized to PTCA (59.7% versus 13.1%).

Subsequently, the National Heart Lung and Blood Institute (NHLBI) in the USA issued a guide to clinical practice that recommended CABG in patients with multi-vessel disease.

Before the publication of the BARI findings, many researchers who studied the long-term course and mortality in diabetics who underwent CABG compared to PTCA, mostly in retrospective studies, had reached conflicting conclusions.[15,16]

The EAST study,[17] a similar but smaller study, included a lesser number of diabetics taking oral anti-diabetic medication (15% versus 19.3% in BARI). After an initial 3-year follow up there was no difference in the overall endpoints between patients randomized to CABG or PTCA (27.3% versus 28.8%), or in mortality considered alone (6.2% versus 7.1%). The only material difference, as in other studies (RITA,[18] CABRI[19]) was the more frequent need for further revascularization in the PTCA group.

After a total follow up of 8 years,[20] a marginally significant difference was found in survival, independent of the therapy initially applied, with CABG being superior (82.7 versus 79.3%). In the diabetic subgroup, although the initial 3- and 5-year follow ups showed similar survival rates, extension of the follow up to 8 years showed that diabetics who were treated with surgical reperfusion had a clear benefit (survival 75.5% versus 60.1%). It is likely that the absence of any differences earlier was due to the small number of diabetics (59) included in the EAST study.

Unluckily, neither the EAST nor the BARI[21] study provided information about the results of effective control of blood glucose levels in diabetic patients.

For non-diabetic patients the findings of all the studies (BARI, EAST, GABI, GABRI, RITA) support the conclusion that the only difference between PTCA and CABG is in the need for further revascularization, since the mortality and the incidence of infarction are similar for the two therapies. Studies comparing CABG with stent implantation (ARTS,[29] SOS[35]) produced equivalent results.

In conclusion, based on the above findings, in diabetic patients with symptomatic multi-vessel disease who are candidates for revascularization the long-term survival is clearly better after CABG. It is rather difficult to give a definitive recommendation, since there are probably many patients with CAD who would also benefit from a PTCA procedure. Furthermore, the protective effect of surgical reperfusion was seen only in patients where the internal mammary artery was used, while in non-diabetic patients the choice of technique has no effect on mortality. One question that remains unanswered is whether diabetics who initially undergo PTCA and need further revascularization should be treated surgically.

It is true that the two major studies mentioned above started around 10 years ago. In the time that has elapsed since then, new, revolutionary techniques have been introduced for the management of ACS. Glycoprotein (GP) IIb/IIIa receptor agonists, stents (especially drug eluting), and the latest antiplatelet medications have contributed to an improvement in the prognosis of patients who undergo PTCA. Studies currently in progress may clarify to what extent these developments improve survival in diabetics.

Bertrand et al[23] studied the angiographic course and prognostic indexes of restenosis 6 months after conventional PTCA in 455 diabetic patients (of whom 25% had ACS). Restenosis and total occlusion were observed in 62% and 13% of the patients, respectively. The following 5 independent predictors of restenosis were identified: angioplasty in a venous graft or bifurcation of a vessel, TIMI flow <3, the degree of residual stenosis immediately after the procedure and the presence of organ damage (nephropathy, neuropathy, retinopathy). An important finding was that the presence of complete occlusion, mainly in patients taking insulin, was accompanied by a reduction in left ventricular ejection fraction. The prothrombotic process in diabetics probably explains the high incidence of vessel occlusion after 6 months,[24,25] as diabetic patients are known to have more frequent lesions with thrombus, which is known to be a predisposing factor for long-term obstruction.[26]

The findings of the above study prove that, in spite of the initial successful outcome of conventional PTCA in diabetic patients, the long-term results are disappointing. This reinforces the case for using newer techniques, especially the parallel administration of IIb/IIIa receptor agonists. Analysis of the subgroups in the EPILOG study[27] showed that the combination of a GP IIa/IIIb inhibitor with PTCA in diabetic patients reduced ischemic events over a 6-month follow up, while the use of stents in a diabetic population was associated with an acceptable risk of restenosis and long-term vessel occlusion (<30% and <5%, respectively).

Similar findings were reported by King et al,[28] who found a high incidence of events in diabetic patients and who seriously questioned the advisability of PTCA in patients with multi-vessel disease under insulin therapy. The authors noted that even though in-hospital mortality was greater in the CABG group (4.99% versus 0.36%) and the overall survival after 5 and 10 years was 78% and 45% for the PTCA group and 76% and 48% for the CABG group, respectively, in insulin-dependent patients the long-term results were clearly better for CABG than for PTCA (5- and 10-year survival 75% and 47% for CABG, 68% and 36% for PTCA, respectively).

It should be underlined that complete revascularization was achieved in only 16% of the insulin-dependent patients who underwent PTCA, compared to 80% for CABG. It is noteworthy that the study makes vague reference to the use of stents, without making it clear what percentage of patients had a stent implanted. It should also be borne in mind that all the studies that compared conventional angioplasty with CABG are of limited value, since they were carried out before the introduction of the newer antiplatelet drugs.

There are very few data from randomized studies comparing PTCA plus stenting with CABG in patients with multi-vessel disease. In 2001 the ARTS randomized study[35] of 1205 patients reported no significant difference between the 2 groups after 12 months, as regards the incidence of major cardiac events. Of course, the need for revascularization was significantly more frequent in patients who underwent PTCA with stent implantation (16.8% versus 3.5%). A sub-analysis of the study, with 208 diabetic patients, showed that stent implantation was accompanied by a smaller rate of event-free survival (63.4%) compared to diabetic patients who underwent CABG (84.4%) or to non-diabetics who had a stent implanted (76.2%).

Van den Brand et al,[30] in a recent publication analyzing the data of the ARTS study, evaluated the relation between full revascularization and adverse events during the first 12 months. They concluded that full revascularization is achieved more frequently following CABG. One year after CABG there was no difference in event-free survival between patients with full or incomplete revascularization. In contrast, after stent implantation the patients with incomplete revascularization needed subsequent surgical treatment more frequently. Undoubtedly, stent implantation in diabetic patients contributed to a better prognosis compared with conventional PTCA. Restenosis at 6 months in diabetic patients after elective stent implantation, according to the findings of the EAST study,[20] was 25% compared to 63% for PTCA alone. The corresponding figures for non-diabetics were 27% and 36%.

Recent data reinforce the hypothesis that in ACS the parallel administration of antiplatelet agents contributes significantly to a reduction in major events and an improvement in long-term prognosis, especially after stent implantation.[31-34] Moreover, as the SOS study[35] showed, the use of intracoronary stents in diabetics is safe and contributes to a reduction in the need for further revascularization (over a 2-year follow up).

Of course, it has to be noted that the frequency of a need for new revascularization remains significantly greater than in the case of CABG (21% versus 6%), even though the incidence of Q-infarction and mortality does not differ significantly between the two groups (9% versus 10%).

The findings were published recently from the multicenter, randomized ERACI II study,[34] which compared the efficacy and safety of CABG with PTCA and stent implantation in symptomatic patients (20% were diabetic) with ACS and multi-vessel disease. The results were encouraging for the stent group, since during the first 30 days those patients had fewer major events compared to the CABG group. Furthermore, during the 2-year follow up the survival rate in the stent group was 96.9% compared to 92.5% for CABG. Also, the incidence of myocardial infarction was clearly lower in the stent group (2.3% versus 6.6%). In contrast, the need for revascularization was greater (16.8% versus 4.8%) than in the patients who underwent CABG. It is well known that in patients with multi-vessel disease the achievement of full reperfusion by angioplasty, even with the use of stents, lags behind that of CABG.

The surgical in-hospital mortality in the above study was greater than in CABRI, BARI or EAST, but the large number of patients with unstable angina, post-infarction angina and coexisting peripheral disease should be taken into account.

Moreover, there are indications that DM is not a significant risk factor for clinical restenosis following stent implantation in patients with unstable angina.[36] Of course, a high percentage of diabetic patients have small coronary vessels. In this category of patients, the restenosis rate (diameter stenosis >50%) after 6 months is clearly greater and exceeds 40%.[37]

A significant proportion of diabetic patients with small vessels are women, in whom the appearance of an unstable coronary syndrome is an independent factor in morbidity.[38]

A number of clinical and angiographic factors are implicated in in-stent stenosis observed in the vessels of diabetics. Among these are the vessel diameter, especially when this is below 2.7 mm, the minimum residual lumen diameter immediately following the procedure, the use of multiple stents and the length of the stent.[39]

Also, the presence of microalbuminuria is an important prognostic factor following percutaneous reperfusion.[40] Studies from the Joslin Diabetic Center have concluded that the incidence of CAD increases dramatically in the presence of diabetic nephropathy.[41] (Figure 4) Diabetic nephropathy is characterized by persistent proteinuria, a reduction in glomerular filtration and arterial hypertension.

Marso et al[40] compared the mortality and the incidence of clinical events following angioplasty in diabetics and non-diabetics with and without proteinuria and found that the mortality after 2 years' follow up was 7.3% and 13.5% for non-diabetics and diabetics, respectively. Similarly, the mortality in the presence of albuminuria was significantly greater (20.3% versus 9.1%), whereas the survival rate in diabetics without albuminuria did not differ from that in non-diabetics.

Furthermore, patients at high risk for CABG with a recent myocardial infarction and a low ejection fraction (<35%) who are not managed with drug treatment have a favorable prognosis following percutaneous coronary intervention (PCI). The AWESOME multicenter study (1995-2000)[42] showed that the long-term findings are comparable for the 2 groups. Survival after CABG and PCI was 90% versus 94% at 6 months and 79% versus 80% at 36 months, respectively. Of course, the use of stents reached a percentage of 54% of lesions overall, climbing from 26% in 1995 to 88% in 1999-2000, while around 11% of the patients were taking IIb/IIIa inhibitors (1% in 1995, 51% in 2000). Furthermore, 70% of the patients in the study who underwent CABG received a left mammary artery graft, 3.2% a right mammary and 2.9% a radial artery graft. In contrast, in the BARI and EAST studies mammary artery grafts were used in 84% and 86%, respectively.

The subgroup of diabetic patients who were included in the AWESOME study were followed for 3 years. The findings were impressive, since no differences in survival were noted between diabetics and non-diabetics, regardless of the treatment used. The authors reported that patients and treating physicians were allowed to choose freely between the two therapeutic approaches. It is likely, as R. Favaloro has stressed,[43] that the two techniques will remain complementary over the course of time.

It is a fact, though, that the data are changing continuously, since the introduction of drug-eluting stents into the daily practice of hemodynamic laboratories is expected to change the manner of therapeutic approach to coronary patients, and especially to diabetics. One of the most important findings of the RAVEL study,[44] in which stents coated with sirolimus were used, referred to 19 diabetic patients. The results after 6 months' follow up were impressive. Restenosis was 0%, compared to 42% for the control group. The need for revascularization of the target vessel was also zero, while regardless of the size of the vessel no thromboses or deaths were observed.

Furthermore, the SIRIUS study,[45] which involved a larger number of diabetic patients (131), found that at 9 months the need for revascularization of the target vessel ranged around 10.3% in the patients with an eluting stent compared to 25% in the control group (conventional stent). Restenosis during the same period was found to be 5.5% versus 17.6%, respectively. More recently (September 2003), the findings of the TAXUS IV study[46] were reported, regarding the use of stents coated with slow release paclixatel (taxol). The restenosis rate after 9 months in the diabetic subgroup (318 patients) who received the new stent was impressively low (6.4% versus 24.4%).

The role of glycoprotein IIb/IIIa inhibitors

The existence of ulcerated atheromatous plaques coexistent with thrombus is the main cause in the pathogenesis of ACS and of ischemic complications in coronary interventions. Inhibitors of GP IIb/IIIa receptors on the platelets are powerful drugs for the prevention of transition to acute myocardial infarction and death.[47]

The early administration of GP IIb/IIIa inhibitors during the treatment of patients with ACS, without ST elevation, has been proved to be beneficial. Additionally, inhibition of the receptors during percutaneous procedures contributes to the protection of the myocardium. Abciximab, tirofiban and eptifibatide achieve comparable levels of inhibition of platelet adhesion and their action has been assessed in a number of studies. Meta-analysis of the CAPTURE,[48] PURSUIT[49] and PRISM-PLUS[50] investigations led to the conclusion that inhibition of platelet adhesion, by administration of aspirin and heparin started immediately following the admission of a patient with ACS to the hospital and continued until the invasive procedure, contributes to a reduction in major complications.

Of course, hemorrhagic complications may occur following the administration of IIb/IIIa inhibitors, but in most cases these are mild and involve the point of arterial puncture.

Diabetic patients with ACS make up a special group with regard to the administration of IIb/IIIa inhibitors, since they are known to have a rather worse course than do non-diabetics, even after stent implantation.[51,52]

The compromised platelet function and thrombocytopathy with concomitant platelet hyperreactivity[53,55] that coexist in DM may comprise the principal mechanism for adverse events. Also, in the presence of DM, the response of the arterial wall is different, while at the same time there are disturbances of the microcirculation and the coronary reserve.[56-58] The administration of GP IIb/IIIa inhibitors is even more effective in diabetic patients with ACS and is associated with a corresponding reduction in the need for revascularization and stent implantation.[59.60]

The first analysis to assess the effect of abciximab on the survival of patients with DM and ACS was published in 2000[61] and referred to comparative data from the EPIC, EPILOG and EPISTENT studies.[62-64]

The administration of abciximab reduced 1-year mortality from 4.5% to 2.5%, while in non-diabetics the reduction was from 2.6% to 1.9%. In patients with insulin-resistant syndrome (diabetes, hypertension and obesity) the mortality was reduced from 5.1% to 2.1%. A similar improvement was seen in insulin-dependent patients (from 8.1% to 4.2%) and in patients with multi-vessel disease (from 7.7% to 0.9%). The results of the study indicate that the combination of abciximab with stenting, which is extremely beneficial in diabetic patients, not only reduces the need for target vessel revascularization[62] but also improves survival. Given the noteworthy reduction in mortality, even after multivessel percutaneous coronary procedures, the authors stress the need for a reexamination of the combination of the latest techniques and CABG.[65-67]

Similar findings emerged from a meta-analysis of the PRISM,[68] PLUS,[50] PARAGON A and B,[69,70] PURSUIT[49] and GUSTO IV[71] trials. Inhibition of GP IIb/IIIa receptors in 6,458 diabetic patients was associated with a significant reduction in 30-day mortality (from 6.2% to 4.6%). In contrast, in 23,672 non-diabetic patients no reduction in mortality was seen (3.0% versus 3.0%). In 1,279 diabetic patients who underwent a percutaneous procedure, the use of IIb/IIIa inhibitors contributed to a reduction in 30-day mortality from 4.0% to 1.2%.[72]

In another case, a subanalysis of the data from the PRISM-PLUS study[73] showed a similar significant decrease in 30-day mortality and infarction, in 322 diabetic patients with ACS, following the administration of the inhibitor tirofiban. A reduction in mortality was also seen in the ESPRIT study,[74] after administration of another inhibitor, eptifibatide, over a 12-month follow up. Diabetic patients needed more frequent target vessel revascularization, a finding in agreement with those of other studies.[75,76] Furthermore, analysis of the data from the TARGET study,[77] which compared abciximab with tirofiban, found that the two drugs had similar results regarding the need for target vessel revascularization at 12 months.[80] These findings, while impressive, are considered to be preliminary and a full presentation of the results will be necessary before certain conclusions can be drawn.

In conclusion, DM, which is present in 20% of patients with ACS and is an independent prognostic factor, is accompanied by more extensive CAD, unstable coronary lesions and increased morbidity. It is clear that the unfavorable course exhibited by diabetics, especially after angioplasty, is due to more frequent restenosis and the more rapid development of latent CAD. The use of stents, especially in combination with GP IIb/IIIa inhibitors, as well as the use of mammary artery grafts, improves the long-term clinical outcome in these patients.

Diabetic patients have a worse survival rate following CABG, in both the short and the long term, than do non-diabetics. The severity of albuminuria is an independent prognostic factor for survival after both percutaneous and surgical reperfusion.

Finally, the findings of studies currently in progress, such as Freedom (multi-vessel implantation of drug eluting stents versus surgical revascularization in diabetics) and BARI 2D (comparative evaluation of strict insulin therapy with and without a free choice of reperfusion technique), are expected to contribute to a better understanding and to help in the selection of the best revascularization strategy in diabetic patients with ACS.

References

1. Malmberg K, Ryden L: Myocardial infarction in patients with diabetes mellitus. Eur Heart J 1988; 9: 256-264.
2. Haffner SM, Lehto S, Pyorala K, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in non diabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339: 229-234.
3. Lebru F, Ducimetiere P, Battaglia S, et al: New diagnostic criteria for diabetes and coronary artery disease: Insights from an angiographic study. J Am Coll Cardiol 2001; 37: 1543-1550.
4. Laakso M: Hyperglycemia and cardiovascular disease in type 2 diabetes. Diabetes 1999; 48: 937-942.

5. Malmberg K, Ryden L, Efendie S, for the DIGAMI Study Group: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction: Effects on mortality at 1 year. J Am Coll Cardiol 1995; 26: 57-65.
6. Ohkubo Y, Kishikawa H, Araki E, et al: Intensive insulin therapy prevents the progression of diabetic noninsulin-dependent diabetes mellitus: a randomized prospective six year study. Diabetes Res Clin Pract 1995; 28: 103-117.
7. Diaz R, Paolasso EA, Piegas LS, et al: Metabolic modulation of acute myocardial infraction. Circulation 1998; 21: 2227-2234.
8. Klepzig H, Kobert G, Matter C, et al: Sulfonylureas and ischaemic preconditioning. Eur Heart J 1999; 20: 439-446.
9. U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-853.
10. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986.
11. Grede P, Vedel P, Larsen N, Jensen GVH, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383-393.
12. Ahmed JM, Mehran R, Dangas G, et al: Predictors of late clinical outcomes in patients with unstable angina undergoing percutaneous coronary intervention. J Am Coll Cardiol 2000; 35: 18A.
13. The BARI Investigators: Influence of diabetes on five year mortality and morbidity in a randomized trial comparing PTCA and CABG in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1997; 96: 1761-1769.
14. Detre KM, Lombardero MS, Brooks MM, et al: The effect of previous coronary-artery bypass surgery on the prognosis of patients with diabetes who have acute myocardial infarction. Bypass Angioplasty Revascularization Investigation Investigators. N Engl J Med 2000; 342: 989-997.
15. Basness GW, Peterson ED, Ohman EM, et al: Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. Circulation 1997; 96: 2551-2556.
16. Weintraub WS, Stein B, Kosinski A, et al: Outcome of coronary bypass surgery versus coronary angioplasty in diabetic patients with multivessel coronary artery disease. J Am Coll Cardiol 1998; 31: 10-19.
17. Kosinski AS, Barnhart HX, Weintraub WS, et al and the EAST Investigators: Five-year outcome after coronary surgery or coronary angioplasty: results from the Emory Angioplasty versus Surgery Trial (EAST). Circulation 1995; 91 Suppl 1: 1-543.
18. The RITA Investigators: Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. Lancet 1993; 311: 573-580.
19. CABRI Trial Participants: First year results of CABRI (Coronary Angioplasty versus Bypass Revascularization Investigation). Lancet 1995; 316: 1179-1181.
20. King S, Kosinski A, Guyton A, et al: Eight-Year Mortality in the Coronary Angioplasty Versus Surgery Trial (EAST). J Am Coll Cardiol 2000; 35: 1119-1121.
21. The BARI Investigators: Seven years outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by Treatment and Diabetic Status. J Am Coll Cardiol 2000, 35; 5: 1124-1129.
22. Friesinger G, Gravin J: Diabetes and the cardiologists: A call to action. J Am Coll Cardiol 2000; 35: 1130-1133.
23. Van Belle, Abolmaali K, Bauters C, et al: Restenosis, late vessel occlusion angioplasty in diabetic patients. J Am Coll Cardiol 1999; 34: 476-485.
24. Aronson D, Bloomgarden Z, Rayfield EJ: Potential mechanisms promoting restenosis in diabetic patients. J Am Coll Cardiol 1996; 27: 528-535.
25. Sobel BE: Potentiation of vasculopathy by insulin. Implications from an NHLBI clinical alert. Circulation 1996; 93: 1613-1615.
26. Bauters C, Lablache JM, McFadden EP, Hammon M, Bertrand ML: Relation of coronary angioplasty findings at coronary angioplasty to angiographic restenosis. Circulation 1995; 92: 2473-2479.
27. Kereiakes DJ, Lincoff M, Miler DP, et al: Abciximab therapy and unplanned coronary stent deployment. Circulation 1998; 97: 857-864.
28. King SB: Coronary artery bypass graft or percutaneous coronary interventions in patients with diabetes: Another nail in the coffin or "Too close to call?" J Am Coll Cardiol 2001; 37: 1016-1018.
29. Serruys PW, Unger F, Sousa JE, et al: Randomized comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001; 344: 1117-1124.
30. Van den Brand MJ, Rensing BJ, Morel MM, et al: The effect of completeness of revascularization on event free survival at one year in the ARTS trial. J Am Coll Cardiol 2002; 39: 559-564.
31. Van Belle E, Bauters C, Hubert E, et al: Restenosis rates in diabetic patients: a comparison of coronary stenting and balloon angioplasty in native coronary vessels. Circulation 1997; 96: 1454-1460.
32. Lincoft AM: Does stenting prevent diabetic arterial shrinkage after percutaneous coronary revascularization? Circulation 1997; 96: 1374-1477.
33. Marso SP, Tanguay JF, Bhatt DL, et al: Optimizing the percutaneous coronary interventional strategy for diabetics. The EPISTENT Experience. Circulation 1997; 98: 1-79.
34. Rodriquez A, Bernardi V, Navia J, et al: Argentine randomized study: Coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple-vessel disease (ERACI II): 30 day and one-year follow up results. J Am Coll Cardiol 2001; 37: 51-58.
35. The SOS Investigators: Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the stent or surgery trial): a randomized controlled trial. Lancet 2002; 360: 965-970.
36. Piraino R, Damonte A, Kirchmann D, et al: Diabetes is not a risk factor for clinical restenosis after coronary stenting. Eur Heart J 2001; 22 (Abstract Suppl.): p. 495.
37. Sueselbeck T, Latsch A, Siry H, et al: Diabetes mellitus is associated with an increased rate of in-stent restenosis in small vessels. Eur Heart J 2001: 22 (Abstract Suppl.): p. 495.
38. Sousa JM, Carralho AC, Lima VE, Hermann LV: Comparison of clinical presentation, FCG, and coronariography in diabetes and nondiabetic women with unstable angina. Eur Heart J 2001; 22 (Abstract Suppl.): p. 723.
39. Sóselhock et al: Role of vessel size as a predictor for the occurrence of in stent restenosis in patients with diabetes. Am J Cardiol 2001; 88: 243-247.

40. Marso SP, Elles S, Tuzcu M, Topol E: The importance of proteinuria as a determinant of mortality following percutaneous coronary revascularization in diabetics. J Am Coll Cardiol 1999; 33: 1269-1277.
41. Krolewski AS, Kosinski EJ, Warram JH, et al: Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 1987; 59: 750-755.
42. Sedlis S, Morrison D, Sethi G, et al: Percutaneous coronary intervention versus coronary bypass graft surgery. Outcome of diabetics in the AWESOME randomized trial and registry. J Am Coll Cardiol 2001; 37: 2 Suppl A, 1A-648A.
43. Favaloro RG: Critical analysis at coronary artery bypass graft surgery: a 30 year journey. J Am Coll Cardiol 1998; 31 (Suppl. B): 1B-63B.
44. Fajadet J, Perrin M, Ban Hayashi E, et al: 210 day follow-up of the RAVEL study: A randomized double blind study with the sirolimus eluting BX Velocity balloon expandable stent in the treatment of patients with de novo coronary artery lesions. J Am Coll Cardiol 2002; 29: Suppl A.
45. Moses JW: The sirolimus-coated BX-Velocity balloon expandable stent (SIRIUS) trial. TCT Meeting. Washington 2002.
46. Natick MA: Taxus IV Drug Eluting Stent Trial TCT Meeting. Washington, 2003.
47. Coler BS: Blockade of platelet GP IIb/IIIa receptors as an antithrombotic energy. Circulation 1995; 92: 2373-2380.
48. The CAPTURE Investigators: Randomized placebo controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429-1435.
49. The PURSUIT Investigators: Inhibition of platelet glycoprotein IIb/IIIa with eptifibitide in patients with acute coronary syndrome. N. Engl J Med 1998; 339: 436-443.
50. PRISM-PLUS Investigators: Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q wave myocardial infraction. N Engl J Med 1998; 338: 1488-1497.
51. Abizaid A, Komowski R and Mintz G/S et al: The influence of diabetes mellitus on acute and late outcomes following coronary stent implantation. J Am Coll Cardiol 1998; 32: 584-589.
52. Elezi S, Kastrati A and Pache J et al: Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 1998; 32: 1866-1873.
53. Iwase E, Tawata M, Aida K, et al: A cross-sectional evaluation of spontaneous platelet aggregation in relation to complication in patients with type II diabetes mellitus. Metabolism 1998; 47: 699-705.
54. Knobler H, Savion N, Shekman B, Kotev-Emeth S, Varon D: Shear-induced platelet adhesion and aggregation on subendothelium are increased in diabetic patients. Thromb Res 1998; 90: 181-190.
55. Tschoepe D, Rossen P: Heart disease in diabetes mellitus: a challenge for early diagnosis and intervention. Exp Clin Endocrinol Diabetes 1998; 106: 16-24.
56. Park SH, Maro SP, Foundl F, et al: Diabetes and the response to arterial injury (abstr). Circulation 1998; 98: 1-8.
57. Akanse T, Yahbee R, Hozumi T, et al: Retinopathy identifies marked influence of coronary flow reserve in patients with diabetes mellitus. J Am Coll Cardiol 1997; 30: 935-941.
58. Yokayama I, Momomura SI, Ohtake T, et al: Reduced myocardial flow reserve in non insulin dependent diabetes mellitus. J Am Coll Cardiol 1997; 30: 1472-1477.
59. Lincoff AM, Cahtt RM, Moliterno DJ, et al: Complementary clinical benefits of coronary artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. N Engl J Med 1999; 314: 319-327.
60. EPISTENT Investigators Marso SP, Lincoff AM, Ellis SG, et al: Optimizing the percutaneous Interventional outcomes for patients with diabetes mellitus. Results of the EPISTENT diabetic study. Circulation 1999; 100: 2427-2484.
61. Bhatt D, Marso S, Lincoff M, et al: Abciximab reduces mortality in diabetics following percutaneous coronary intervention. J Am Coll Cardiol 200; 35: 922-928.
62. The EPIC investigation: Use of a monoclonal antibody directed against the platelet IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994; 330: 956-961.
63. The EPILOG Investigators: Platelet glycoprotein IIb/IIIa receptor blockade and low dose heparin during percutaneous coronary revascularization. N Engl J Med 1997; 336: 1689-1896.
64. The EPISTENT Investigators (Evaluation of Platelet IIb/IIIa Inhibition for Stenting): Randomized placebo-controlled and balloon-angioplasty controlled trial to access safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade. Lancet 1998; 352: 87-92.
65. Goldberg S, Savage MP, Fischman DL: The interventional cardiologist and the diabetic patients. Have we pushed the envelope too far or not far enough? Circulation 1996; 94: 1804-1806.
66. Abizaid A, Costa MA, Centemero M, et al, on behalf of the ARTS Investigators: Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients. Insights from the Arterial Revascularization Therapy Study (ARTS) Trial. Circulation 2001; 104: 533-538.
67. Kuntz RE: Importance of considering atherosclerosis progression when choosing a coronary revascularization artery: the diabetes percutaneous transluminal coronary angioplasty dilemma. Circulation 1999; 99: 847-851.
68. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators: A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998; 338: 1498-1505.
69. The PARAGON Investigators. Platelet IIb/IIIa Antagonism for the reduction of acute coronary syndrome events in a global organization network: International, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin or both in unstable angina. Circulation. 1998; 97: 2386-2395.
70. Moliterno DJ: Patient-specific dosing of IIb/IIIa antagonists during acute coronary syndromes: rationale and design of the PARAGON B Study. The PARAGON B International Steering Committee. Am Heart J 2000; 139: 563-566.
71. Simoons ML: Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularization: the GUSTO IV-ACS randomized trial. Lancet 2001; 357: 1915-1924.
72. Roffi M, Chew D, Mukherjee D. et al: Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST segment-elevation acute coronary syndromes. Circulation 2001; 104: 2707-2771.
73. Theroux P, Alexander J Jr, Pharand C, et al: Glycoprotein IIb/IIIa receptor blockade improves outcomes in diabetic patients presenting with unstable angina/non-ST-elevation myocardial infraction: Results from the Platelet Receptor Inhi-

bition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study. Circulation. 2000; 102: 2466-2472.
74. The ESPRIT Investigators: Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomized, placebo controlled trial. Lancet 2000; 356: 2037-2044.
75. Stein B, Weintraub WS, Gebhart SP, et al: Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. Circulation. 1995; 91: 979-989.
76. Kleiman NS, Lincoff AM, Kereiakes DJ, et al: Diabetes mellitus, glycoprotein IIb/IIIa blockade, and heparin: evidence for a complex interaction in a multicenter trial Circulation 1998; 97: 1912-1920.
77. Roff M, Moliterno DT, Meier B, et al: Impact of different platelet glycoprotein IIb/IIIa receptor inhibitors among diabetic patients undergoing percutaneous coronary intervention: do Tirofiban And ReoPro Give similar Efficacy outcomes Trial (TARGET) 1-year follow-up. Circulation 2002; 105: 2730-2736.