Arithrombotic drug therapy to maintain graft patency after coronary artery bypass surgery
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Coronary artery bypass surgery has improved the quality of life in patients with severe disabling angina. A favourable effect on life expectancy has been demonstrated only in a subgroup of these patients. The results of surgery have been improved with time, mainly due to changes in surgical technique, like the procedure of preparing grafts and the introduction of arterial bypass conduits. The number of surgical patients is still rising, despite widespread and extending application of percutaneous transluminal coronary angioplasty. However, the obtained benefit has been limited by the occurrence of graft occlusion, due to thrombosis and intimal proliferation in the first year and progressive atherosclerosis after the fifth postoperative year. Endothelial injury by manipulation and ischemia of the graft is considered to be the main cause of thrombosis and intimal proliferation. Whether this mechanism contributes to the development of atherosclerosis remains to be clarified. Atherosclerosis, being a more common finding in vein grafts, might be explained alternatively as response of the vessel wall to the pulsatile blood flow.

There is convincing evidence that early vein graft patency is improved by antithrombotic drug therapy, provided that this is started before surgery or within 24 hours postoperatively and is continued for at least one year. The effects of antithrombotic drug therapy on long-term vein graft patency have not been studied. Because internal mammary artery (IMA) grafts have shown superior long-term patency, these are preferred to vein grafts. It has to be noticed that their superiority has been derived from studies in patients who underwent coronary artery bypass surgery over a long period that started about 20 years ago. It is questionable whether the results of previous studies represent today's surgery, given the more recent introduction of antithrombotic drug therapy and improved vein graft patency. This thesis deals with the effects of various antithrombotic drug regimens on one-year graft patency and clinical outcome in patients who underwent coronary artery bypass surgery, using either vein grafts only or both IMA grafts and vein grafts.

An overview of previous studies on the prevention of vein graft occlusion by antithrombotic drugs is given in chapter 1. It contains not only those studies that had been reported before the start of the here presented study in 1987. Similar efficacy was demonstrated by placebo-controlled clinical trials, comparing 325 mg aspirin per day with 975 mg aspirin per day. An additional benefit of dipyridamole in combination with aspirin remained controversial, whereas the results of oral anticoagulant therapy were not conclusive. A wide variety of drug regimens was applied in clinical practice, based on their supposed rather than established efficacy.

Objectives and design of the "prevention of Coronary Artery Bypass graft occlusion by Aspirin, Dypiridamole, and Acenocoumarol/phenprocoumon Study" (CABADAS) are described. This prospective, randomized multicenter trial was conducted to assess the relative efficacy and safety of aspirin (50 mg per day), aspirin plus dipyridamole, and oral anticoagulants with respect to graft patency and clinical outcome.

The primary results of the study are reported in chapter 2. Vein graft occlusion rates showed no statistically significant differences, comparing aspirin plus dipyridamole and oral anticoagulants, respectively, with aspirin alone. A trend to improved graft patency
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was observed in patients who received aspirin plus dipyridamole. In particular patency of grafts to small sized coronary arteries was favoured. Since these grafts contained a majority of all grafts, this benefit might be of clinical relevance. By contrast with this limited beneficial effect, there was a statistically significant and clinically relevant increase in the overall risk of major clinical events (myocardial infarction, thrombosis, major bleeding, and death) in patients who were treated with aspirin plus dipyridamole. Compared with aspirin, oral anticoagulants provided no benefit with respect to graft occlusion and clinical outcome. Thus, a low dose of aspirin may be preferred to prevent vein graft occlusion during the first year after coronary artery bypass surgery, the more because of additional advantages, like practicality and costs.

A similar analysis was done in patients who received IMA grafts in addition to vein grafts (chapter 3). Occlusion rates of IMA grafts were obviously lower than those of vein grafts, mentioned in chapter 2. No differences in graft patency between the three treatment groups were demonstrated. Aspirin plus dipyridamole therapy, as compared with aspirin, was associated with an increased overall risk of clinical outcome events. Since IMA grafts apparently have an excellent long-term patency, it may be wondered whether antithrombotic drug therapy is required at all. However, vein grafts are implanted frequently in addition to IMA grafts, like in the patients of this study. Therefore, the need for antithrombotic drug therapy primarily depends on the simultaneous application of vein grafts. If both grafts are used, aspirin therapy seems to be sufficient and may be preferred to both other drug regimens.

The supposed superiority of IMA grafts has been derived from previous studies. Reported differences in graft patency and clinical outcome in favour of IMA grafts, as compared with vein grafts, may have been biased by selection of patients and an inappropriate comparison of IMA grafts versus vein grafts in these studies, as clarified in chapter 4. An analysis of the available data from the present trial aimed a more proper comparison. Indeed, an obvious difference was found by comparing patency rates of IMA grafts and vein grafts according to the methods of previous studies. Differences became much less pronounced or even disappeared by considering IMA grafts and vein grafts with the same graft characteristics, like location of the graft and internal diameter of the grafted coronary artery. A multivariate analysis, using the random effects logistic regression model, showed no relationship between graft material (vein or arterial) and graft patency, by contrast with other graft characteristics. The previously reported differences are probably due to a comparison of IMA grafts that were commonly placed to the left anterior descending coronary artery versus vein grafts to the remaining coronary arteries. Grafts to the left anterior descending coronary artery showed higher patency rates, for both vein and IMA grafts. Thus, the observed difference was predictable. Of course, the present analysis contained only one-year follow-up. A five to ten-years follow-up is required to assess differences in long-term graft patency, which might be expected due to progressive atherosclerosis of vein grafts after the fifth postoperative year. By contrast with previous studies, no differences in one-year clinical outcome were observed in patients who received only vein grafts versus those in whom both vein grafts and IMA grafts were implanted. Again, a long-term follow-up is required to establish equality of these grafts in this respect. It might be assumed that an intrinsic difference between IMA grafts and vein grafts, particularly as result of antithrombotic drug therapy. Evidence of the control by the majority of patients. Patients treated within the predefined target International Normalised Ratio (INR). The question raised by this study is the presence of an increase in the overall risk of clinical events compared with patients in whom the INR was kept between 2.5 and 3.5. However, a long-term follow-up is required to establish equality of these grafts in this respect. The absence of non-inferiority of one-year patency may be a result of the fact that this study was not adequately powered for this outcome. The absence of non-inferiority of one-year patency may be a result of the fact that this study was not adequately powered for this outcome. The absence of non-inferiority of one-year patency may be a result of the fact that this study was not adequately powered for this outcome.
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Grants in addition to vein grafts in addition to vein grafts more than those of vein grafts, between the three treatments, as compared with aspirin, the same events. Since IMA grafts wondered whether antithrombotic drugs are implanted frequently in therefore, the need for antithrombotic application of vein efficient and may be preferred

previous studies. Reported IMA grafts, as compared with patients and an inappropriate is clarified in chapter 4. An more proper comparison. of IMA grafts and andes became much less dd vein grafts with the same ueter of the grafted coronary anastomosis (2.8-4.8 International Normalized Ratio (INR)). The question raised whether improved anticoagulation would have resulted in a decrease in occlusion rate. This was the subject of a subgroup analysis, reported in chapter 5. It was demonstrated that adequate anticoagulation in these patients ranged from 49 to 71% dependent on the method that was used to express intensity and stability of anticoagulation. Comparing patients who spent 70% or more of treatment time versus less than 70% of treatment time within the target range of anticoagulation, occlusion rates showed no difference. To estimate the optimum level of anticoagulation, occlusion rates for various levels of anticoagulation between 1.0 and 4.8 INR were compared in patients in whom these levels were observed for 70% or more of time. Occlusion rates appeared to be similar to INR ranges 1.8-3.8 and 2.8-4.8, respectively. Assuming that one-year patency is related to the level of anticoagulation in the first weeks to months of surgery, one-year occlusion rates were analyzed with respect to the level of anticoagulation that was observed at hospital discharge, for the first, the first three, and the remaining nine months of follow-up. There was no evidence of improved graft patency in patients who showed more intensive anticoagulation in the early postoperative period. Thus, a level of anticoagulation above 1.8 INR for 70% or more of the first postoperative year seems to be sufficient to maintain vein graft patency.

The main reason to start antithrombotic drug therapy after rather than before coronary artery bypass surgery, is an increase in blood loss during operation that has been associated with the preoperatively started administration of these drugs. Especially the risks of blood transfusion have emphasized the need for procedures to reduce blood loss. Aprotinin has demonstrated the ability of a remarkable reduction of blood loss and transfusion requirement. However, in coronary artery bypass surgery, improved hemostasis by this drug might result in an increased risk of thrombosis i.e. graft occlusion and myocardial infarction. Chapter 5 deals with this issue. The risk-benefit ratio of aprotinin therapy was estimated by comparing blood loss, transfusion requirement, graft patency, and clinical outcome with respect to thrombotic events in patients who were treated peroperatively with aprotinin versus those who did not receive this drug. Blood loss and transfusion requirement showed to be significantly lower in the aprotinin group. Vein graft occlusion was observed more frequently in the aprotinin group. The observed difference in occlusion rates by distal anastomosis did not achieve, although approached, statistical significance. By contrast, a significant difference was demonstrated considering patients with graft occlusion. This apparent discrepancy is probably due to the small number of patients in the aprotinin group. Myocardial infarction was observed more frequently in the aprotinin group. This finding is in agreement with the results of the only previous study that was properly designed to detect the occurrence of this event, although it was not adequately powered to demonstrate statistical significance of the observed difference. The absence of non-conclusive results does not establish the safety of aprotinin therapy. Evidence of the contrary from this and the mentioned previous study necessitates
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more, properly designed clinical trials. Waiting for the results of such trials, aprotinin should not be recommended for routine application in coronary artery bypass surgery.

Conclusions

1. A low dose of aspirin (50 mg per day) is sufficient to retain vein grafts patent during the first year after coronary artery bypass surgery. Addition of dipyridamole to aspirin might improve especially patency of grafts to small sized coronary arteries. However, by contrast with this limited benefit, dipyridamole increases the risk of major clinical events. Oral anticoagulants provide no benefits, as compared with aspirin. Thus, aspirin is preferrable in the prevention of vein graft occlusion.

2. If antithrombotic drug therapy is worthwhile in the prevention of internal mammary artery graft occlusion, a low dose of aspirin may be preferred.

3. There is no evidence of a difference in one-year patency of vein grafts versus internal mammary artery grafts. Clinical outcome during the first postoperative year is in agreement with equality in graft patency.

4. Oral anticoagulant therapy is sufficient to prevent vein graft occlusion if the level of anticoagulation is maintained above 1.8 INR for at least 70% of time during the first year after coronary artery bypass surgery.

5. Peroperative administration of aprotinin reduces blood loss and transfusion requirement, but there is evidence of an increase in one-year vein graft occlusion rate, whereas aprotinin therapy may be associated with an increased risk of perioperative myocardial infarction.

Despite the benefit of current antithrombotic drug therapy, graft occlusion remains in a substantial proportion of the patients who undergo coronary artery bypass surgery. It has to be noticed that occlusion of a graft does not always result in a deterioration of the patient's clinical condition. Only a long-term clinical follow-up enables to assess the results of surgery, considering the original purpose of this procedure. Graft occlusion due to technical failure will never be completely avoidable. Newly developed antithrombotic drugs might be more effective than aspirin and oral anticoagulants. However, efficacy and safety of these drugs are closely related, and clinical trials are required to assess their clinical superiority, as compared with aspirin. Finally, it is recommendable to evaluate the here presented patients five to ten years after surgery to establish the long-term results of today's coronary artery bypass surgery.