Fourteen-Year Follow-Up From CABADAS: Vitamin K Antagonists or Dipyridamole Not Superior to Aspirin

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Background. **Secondary prophylaxis using aspirin is standard of care after coronary artery bypass graft surgery. Limited data are available for long-term results. We evaluated the effect of aspirin, aspirin with dipyridamole, and vitamin K antagonists (VKA) on 14-year clinical outcome of patients included in the Prevention of Coronary Artery Bypass Graft Occlusion by Aspirin, Dipyridamole, and Acenocoumarol/Phenprocoumon Study (CABADAS).**

Methods. **All 726 Dutch patients for whom antithrombotic therapy with aspirin (n = 248), aspirin with dipyridamole (n = 234), or VKA (n = 244) was randomly allocated were included. The primary endpoint was occurrence of major adverse cardiac events (MACE). Outcomes were retrospectively evaluated during 14-year follow-up.**

Results. **Cumulative incidences for MACE over 14 years were 49%, 50%, and 59% for patients treated with aspirin, aspirin with dipyridamole, and VKA, respectively. Although the overall occurrence of MACE did not significantly differ among the three treatment groups ($p = 0.12$), patients treated with VKA were at higher risk of MACE than patients treated with aspirin with dipyridamole (hazard ratio 1.3, 95% confidence interval: 1.0 to 1.8, $p = 0.041$) and patients treated with aspirin alone (hazard ratio 1.1, 95% confidence interval: 0.86 to 1.5, $p = 0.37$). This difference was attributed to an increased risk of repeat revascularization in patients treated with VKA, without any differences in cardiac death and myocardial infarction among the three treatment groups. However, the observed high rate of repeat revascularization in patients treated with VKA could reflect an a priori increased probability for repeat revascularization due to the specific conditions surrounding VKA therapy (ie, more intense patient–doctor contacts).**

Conclusions. **This study with 14-year clinical outcome provides further evidence for the use of aspirin as secondary prophylaxis after coronary artery bypass graft surgery.**

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Several prospective controlled clinical trials have evaluated the efficacy and safety of antithrombotic drug therapies for secondary prophylaxis after coronary artery bypass graft surgery (CABG) to prevent vein graft closure [1]. This resulted in a high level of evidence, identifying aspirin as standard of care [2, 3]. To maximize the effect of anticoagulant treatment, it must be initiated already early after surgery [4-6]. In this respect, current guidelines stipulate the initiation of aspirin within 48 hours after surgery and to be continued indefinitely [4, 5]. When started more than 48 hours after surgery, the efficacy of aspirin is hampered and early graft occlusion more frequently observed [7].

One of the clinical trials was CABADAS (Prevention of Coronary Artery Bypass Graft Occlusion by Aspirin, Dipyridamole and Acenocoumarol/Phenprocoumon Study). The CABADAS trial evaluated the effect of aspirin, aspirin with dipyridamole, and vitamin K antagonists (VKA) on 1-year graft patency and early clinical outcome. The CABADAS study concluded that there was no convincing evidence that the addition of dipyridamole to a low dose of aspirin improves 1-year vein graft patency after coronary artery bypass grafting. Oral anticoagulants, compared with aspirin, provided no benefit [8]. (A complete list of the CABADAS investigators has been published in van der Meer and colleagues [8]).

In many of the clinical trials that contributed to the evidence of aspirin as primary choice for secondary prophylaxis after CABG, data on long-term clinical outcome are limited. As in CABADAS, mainly early effects on graft patency and short-term and midterm clinical outcome are available. Therefore, in the present study, we evaluated the clinical outcome of patients included in the CABADAS study after an extended follow-up for as long as 14 years. These patients were originally treated with aspirin, aspirin with dipyridamole, or VKA.

Patients and Methods

The extended CABADAS study is a retrospective follow-up study involving 726 Dutch participants of the

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†Professor Dr. Jan van der Meer recently died after a sudden illness.

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CABADAS study. A priori, it was decided to only include the Dutch participants for the extension of the CABADAS study. The original CABADAS study was an international multicenter randomized controlled clinical trial evaluating the effects of low- dose aspirin, aspirin combined with dipyridamole, or VKA on graft patency and clinical outcome at 1 year. In this study, 912 patients were evaluated after 1 year of study treatment. The design of the study is described in great detail elsewhere [8]. Initial study protocol was approved by the Ethics Committee of each participating center, and all patients gave written informed consent.

For the extended long-term follow-up, approval from the local Ethics Committee was obtained. Individual patient data were collected without patient identification information. Owing to the retrospective nature of the follow-up study, the need for additional written informed consent was waived.

Patients

All patients underwent elective CABG for disabling angina between July 1987 and August 1990. Surgery was performed using routine techniques in each participating center. They all received saphenous vein grafts, and in addition, internal mammary artery (IMA) grafts could be used at the discretion of the surgeon. Heparin, administered during surgery, was antagonized by protamine sulphate at the end of the procedure, unless it was continued because of the introduction of an intraaortic balloon pump. The main exclusion criteria were: age more than 70 years, previous or concurrent cardiac surgery, unstable angina at the time of surgery (within 2 days) or myocardial infarction within 7 days before surgery, and severe concomitant disease.

Randomization

Study treatment was initiated after random allocation, namely, aspirin (50 mg once per day), aspirin with dipyridamole (200 mg twice daily), or VKA (acenocoumarol or phenprocoumon) to all eligible patients before surgery. To ensure a balanced treatment in all participating hospitals, allocation was stratified by study site.

Follow-Up

After discharge from the hospital, patients were seen for the duration of 1 year at 3-month intervals. The extended long-term follow-up was retrospectively performed for all patients until June 2002, through telephone interviews of the patients using a standard questionnaire and by reviewing the medical files of their cardiologists or general practitioners. This evaluation was performed for the first time 2 to 3 years after surgery and was repeated 12 years thereafter. In six of the seven participating centers, ascertainment of the status of every patient in the original cohort was completed within 2.5 months. In one center, this was delayed by 2 months because of logistical reasons, resulting in an overall closing interval of 4.5 months.

Clinical Endpoints

The primary endpoint of the extended follow-up study was the composite of major adverse cardiac events (MACE), namely, cardiac mortality, myocardial infarction, and coronary repeat revascularization. Cardiac mortality was defined as mortality due to acute myocardial infarction, acute cardiac arrest, sudden death, and mortality caused by progressive congestive heart failure. In case of an unknown cause of death, it was classified as cardiac death. For myocardial infarction, pathologic Q waves had to be present on the electrocardiogram in combination with creatine phosphokinase and creatine phosphokinase–myocardial band serum levels that exceeded the upper limits of normal ranges. Repeat revascularization was defined as percutaneous coronary intervention or redo CABG during follow-up.

From the original CABADAS study, patients' characteristics, general and disease-specific medical history, and clinical outcome events were available for as long as 1 year after discharge. Adjudication of these events was performed by a blinded classification committee, without knowledge of the patient's treatment assignment.

Anticoagulation Data

Patients allocated to VKA therapy were referred to specialized thrombosis services for frequent control of the level of anticoagulation. The VKA of choice was acenocoumarol or phenprocoumon. The target range used at the time of the original study was international normalized ratio 2.8 to 4.8.

Statistical Analysis

The primary objective of the study was to evaluate the effect of three antithrombotic drugs on long-term clinical outcome in patients who underwent CABG for disabling angina. Differences between groups were evaluated by survival analysis using an intention-to-treat approach. In this, patients were evaluated by their originally allocated treatment. The event-free survival was graphically depicted using the method of Kaplan-Meier. A multivariable Cox proportional hazards regression analysis was performed to estimate adjusted hazard ratios (HR). Predefined risk factors for MACE were age, sex, body mass index, smoking, diabetes mellitus, hypertension, hypercholesterolemia, history of arterial thrombosis, Canadian Cardiovascular Society (CCS) classification, concomitant cardiovascular medication, severity of vessel disease, type of grafts used (vein or arterial), and number of grafts used. After initial univariate analysis, all those variables associated with MACE at a level of $p = 0.10$ were considered for the multivariable analysis. A manual backward selection strategy was used the reduce to model to a final model with significant risk indicators at the level of $p = 0.05$.

Secondary survival analyses were performed on separate components of MACE using the same strategy as in the primary analysis.

All analyses performed to test the (null) hypothesis of no differences between groups were two-sided. A p value