Postoperative clopidogrel improves mid-term outcome after off-pump coronary artery bypass graft surgery: a prospective study

Ahmet Tayfun Gurbuz a,b,*, Ayhan A. Zia b, Ali Can Vuran a, Haiyan Cui c, Aydin Aytac a

a Department of Cardiothoracic Surgery and Cardiology, Anadolu Foundation Healthcare System, Gebze Kocaeli, Turkey
b Department of Cardiology and Cardiothoracic Surgery, Tucson Medical Center, Tucson, AZ, USA
c Department of Biometrics, Arizona Cancer Center, University of Arizona, Tucson, AZ, USA

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Abstract

Objective: Clopidogrel decreases recurrent ischemic events and improves intracoronary stent patency. There are scarce data on the effect of short-term and long-term clopidogrel on symptom recurrence and adverse cardiac events following off-pump coronary artery bypass graft surgery (OPCAB).

Methods: Postoperative antiplatelet medication use was prospectively evaluated in 591 OPCAB patients. Clopidogrel was administered for 30 days in 186 patients and 139 received long-term clopidogrel (mean 33.6 \pm 12.0 months) in addition to aspirin. Follow-up was 37.7 \pm 13.4 months. Symptom recurrence (angina and congestive heart failure), adverse cardiac events (myocardial infarction, coronary reintervention, and sudden cardiac death), and overall mortality were prospectively recorded. Multivariate Cox regression analysis was used to evaluate predictors of end points.

Results: There was no difference with respect to preoperative risk factors between patient groups. In the multivariate analysis, postoperative clopidogrel independently decreased symptom recurrence (p < 0.0001, OR 0.3 [0.15—0.99]; 95% CI) and adverse cardiac events (p < 0.0001, OR 0.2 [0.10—0.45]; 95% CI). Clopidogrel receivers had significantly lower angina recurrence, myocardial infarction, coronary reintervention, and sudden cardiac death during follow-up. There was no difference in the incidence of end points between short-term (30 days) and long-term receivers of the drug. There were 17 bleeding complications (4 major and 13 minor) in 15 patients during the follow-up period. Of the 15 patients, 6 were on clopidogrel in addition to aspirin (1.8%) while the remaining 9 were on aspirin (3.3%) only at the time of bleeding (p = 0.8).

Conclusions: Clopidogrel therapy was independently associated with decreased symptom recurrence and adverse cardiac events following OPCAB. Extending clopidogrel use beyond 30 days did not have a significant effect on defined end points.

Keywords: Clopidogrel; Off-pump CABG; Outcome

1. Introduction

Antiplatelet therapy has been proven to increase vein graft patency [1,2] and to reduce major adverse cardiac events after coronary artery bypass graft surgery (CABG) [3]. Aspirin has been used for many years as the sole antiplatelet agent for this purpose. Aspirin, however, is a rather weak antiplatelet agent and a number of adverse cardiovascular events still occur during treatment with this medication [4]. A number of patients do not develop predicted platelet inhibition despite being on aspirin. Hence, aspirin resistance is more common than realized [5]. Clopidogrel, a new thionopyridine derivative, inhibits ADP-induced platelet aggregation and has potent antiplatelet action. Clopidogrel when combined with aspirin has been shown to decrease platelet thrombus formation in prosthetic vascular grafts as well as in endarterectomized arteries in experimental studies [6]. Clopidogrel has also been shown to decrease vascular death, myocardial infarction (MI), stroke, and rehospitalization when used in patients with a history of prior cardiac surgery [3]. Off-pump CABG has gained popularity in the last decade; however, concerns remain regarding decreased graft patency and increased mid-term reintervention rates [7,8].

Clopidogrel was used in a small number of patients following off-pump CABG, and it was found to decrease thromboembolic events, myocardial infarction, stroke, and revascularizations in 3 months [9]. There are however no mid-term or long-term follow-up data on the effect of clopidogrel on the incidence of symptom recurrence and adverse cardiovascular events following off-pump CABG.

2. Patients and methods

We evaluated 591 consecutive patients who underwent isolated off-pump CABG by a single surgeon (A.T.G) between
2000 and 2004 as a prospective observational study. The surgical team has adopted off-pump CABG in early 2000 as the revascularization technique in all patients referred for CABG. There were four conversions to on-pump CABG during the same interval, which were also included in the study.

Mean patient age was 67.6 ± 10.7 years and 36% were female. Preoperative Canadian Cardiovascular Society (CCS) angina classes were I and II in 376 patients, III in 111 patients and IV in 61 patients. Postoperative CCS angina classes were I and II in 17 patients and III in 1 patient. There were no patients in CCS class IV angina postoperatively.

The remaining patient characteristics are listed in Table 1. Procedures were carried out with full-length median sternotomy and full-dose heparinization. Saphenous vein grafts and radial arteries were harvested by full-exposure incisions. A suction-stabilizing device (Octopus10 Tissue Stabilizer, Medtronic Inc., Minneapolis, MN, USA) was used for all anastomoses. Intracoronary shunts (Flo-Thru Shunt, Synovis Surgical Innovations, St. Paul, MN, USA) were used when deemed necessary by the surgical team. Heparin was partially reversed for a target-activated clotting time of 180 s. Graft flows were evaluated using a hand-held Doppler probe before and after the administration of protamine. Grafts lacking a prominent diastolic augmentation were immediately revised. Aspirin (325 mg) was administered in the first 6 h postoperatively. Starting June 2001, we added clopidogrel (75 mg) on the first postoperative day without a loading dose in addition to aspirin (clopidogrel receivers) and continued thereafter for 30 days or longer. Aspirin dose was decreased to 81 mg when combined with clopidogrel. A group of patients continued to receive clopidogrel after the initial 30 days in combination with aspirin (long-term clopidogrel receivers). Statin therapy was administered to all patients within first 24 h and continued after their discharge. Perioperative diltiazem (0.25–0.50 μg/kg per minute) was used in all patients who received RA grafts and continued orally (180 mg/day diltiazem or long acting nitrate 30–60 mg/day) for a minimum of 6 weeks following discharge.

Patients were followed prospectively through cardiologists, primary care physicians, and hospital records as well as direct phone contact. Social Security Death Registry Database was searched for patients who could not be contacted or were lost to follow-up. Follow-up was complete in all 591 patients.

Recurrent angina was defined as chest pain classified by Canadian Cardiovascular Society class II or higher; myocardial infarction was defined as increase in serum troponin T levels higher than 3.9 μg/l 24 h or 3.4 μg/l 48 h after surgery with or without Q waves on the EKG; congestive heart failure was defined as new onset shortness of breath, peripheral edema, and systolic or diastolic dysfunction on the echocardiogram with/without pleural effusions.

All cardiac-related events and mortality data were collected including recurrent angina, acute myocardial infarction, congestive heart failure, any repeat coronary intervention (PCI and redo CABG), and cardiac and noncardiac deaths. Angina, myocardial infarction, and new onset congestive heart failure were defined as symptom recurrence. Adverse cardiac events were defined as MI, coronary reintervention, and any cardiac-related mortality including sudden cardiac death.

Continuous data are presented as mean and ± standard deviation (SD) and constant values are presented as absolute numbers. Chi-square and Fisher's exact tests were used to compare paired data. A p-value of <0.05 was used to determine statistical significance. Multivariate stepwise Cox regression analysis was used to analyze the effect of each risk factor on the defined end points and hazard ratios were calculated. All statistical analyses were performed using SPSS Statistical Software for Windows 10.0 (SPSS Inc., Chicago, IL, USA). Survival curves were constructed using Kaplan–Meier method.

![Table 1](https://example.com/table1.png)


**" p < 0.01."
3. Results

Mean number of grafts was 3.4 ± 1.0. A total of six grafts were revised intraoperatively in five patients due to poor graft flow on Doppler interrogation. RA grafts were used mostly for circumflex (CX) and diagonal territory and SV grafts were used to graft right coronary artery (RCA) branches. Mean chest tube output was 910 ml in the clopidogrel group and 1027 ml in the non-clopidogrel group (p = 0.46). Major perioperative complications were reoperation for bleeding in nine patients (five clopidogrel group and four in non-clopidogrel group, p = 0.22), cerebrovascular events in five, respiratory failure in five, renal failure requiring dialysis in three, and myocardial infarction in two. There were seven perioperative deaths.

Postoperative clopidogrel was administered in addition to aspirin in 325 patients (clopidogrel receivers); 266 patients received postoperative aspirin only (non-clopidogrel receivers). The preoperative risk factors, intraoperative variables, including graft types and numbers, as well as percentage of postoperative statin use were compared between the groups who received clopidogrel receivers and non-receivers (Tables 1 and 2). Follow-up was shorter in the clopidogrel group since these patients were included later into the study.

Of the 325 patients who received clopidogrel, 139 patients received the medicine longer than 30 days (mean 33.6 ± 12.0 months) (long-term clopidogrel receivers), whereas 186 received the drug only for 30 days (short-term clopidogrel receivers). Comparison of long-term and short-term clopidogrel receivers showed no significant difference with respect to preoperative risk factors, intraoperative variables as well as percentage of postoperative statin use. A group of patients received neither aspirin nor clopidogrel (27 patients) due to contraindication or concomitant Coumadin therapy. Postoperative statins were used in 391 patients (66.1%).

Mean follow-up interval was 37.7 ± 13.4 months. There were 17 bleeding complications (4 major and 13 minor) in 15 patients during the follow-up period. Antiplatelet therapy had to be stopped temporarily in five patients and permanently in two patients. Of the 15 patients, 6 were on clopidogrel in addition to aspirin (1.8%) while the remaining 9 were on aspirin (3.3%) only at the time of bleeding (p = 0.8). There were two major and five minor bleeding events in the clopidogrel group and two major and eight minor bleeding events in the aspirin-only group.

Twenty-nine patients developed recurrent angina 3–38 months after the procedure. New onset congestive heart failure was diagnosed in five patients. There were nine MI (six in grafted areas and three in non-grafted areas). Repeat coronary interventions were performed in 20 patients during follow-up (18 PCI and 2 reoperative CABG). Four PCIs were to the bypass grafts (all SV) and nine were to the native coronary arteries that were supplied by the occluded grafts (two had SV and seven had RA). Primary PCI was performed in five coronary arteries (two CX and three RCA) that were not bypassed previously. Two patients underwent reoperation at other institutions. There was no peri-procedure mortality for those needing reintervention.

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes (n = 325)</th>
<th>No (n = 266)</th>
<th>x²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest tube output (ml)</td>
<td>910</td>
<td>1027</td>
<td>0.977</td>
<td>0.225</td>
</tr>
<tr>
<td>Graft number ≥ 3</td>
<td>280 (86.2%)</td>
<td>198 (74.4%)</td>
<td>12.988</td>
<td>0.001</td>
</tr>
<tr>
<td>ITA</td>
<td>311 (95.7%)</td>
<td>253 (95.1%)</td>
<td>0.113</td>
<td>0.737</td>
</tr>
<tr>
<td>Radial artery graft</td>
<td>224 (68.9%)</td>
<td>174 (65.4%)</td>
<td>0.819</td>
<td>0.365</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>270 (83.0%)</td>
<td>219 (82.3%)</td>
<td>0.057</td>
<td>0.811</td>
</tr>
<tr>
<td>LAD</td>
<td>309 (95.0%)</td>
<td>257 (96.6%)</td>
<td>0.856</td>
<td>0.355</td>
</tr>
<tr>
<td>Circumflex</td>
<td>288 (88.6%)</td>
<td>237 (89.0%)</td>
<td>0.034</td>
<td>0.853</td>
</tr>
<tr>
<td>RCA</td>
<td>275 (84.6%)</td>
<td>218 (81.9%)</td>
<td>0.749</td>
<td>0.387</td>
</tr>
<tr>
<td>Intracoronary shunt use</td>
<td>249 (76.6%)</td>
<td>208 (78.1%)</td>
<td>0.208</td>
<td>0.648</td>
</tr>
<tr>
<td>Postoperative statin</td>
<td>221 (68.0%)</td>
<td>170 (63.9%)</td>
<td>1.093</td>
<td>0.296</td>
</tr>
<tr>
<td>Postoperative tobacco use</td>
<td>9 (2.8%)</td>
<td>17 (6.4%)</td>
<td>4.562</td>
<td>0.033*</td>
</tr>
</tbody>
</table>

ITA: internal thoracic artery, LAD: left anterior descending artery, RCA: right coronary artery.

*p < 0.05.

Multivariate Cox regression analysis was performed to identify the effect of preoperative variables, intraoperative and postoperative factors on symptom recurrence, adverse cardiac events, and mortality. Postoperative clopidogrel use significantly decreased symptom recurrence (p < 0.0001, OR 0.3, 0.15–0.99; 95% CI) as well as statin use (p < 0.0001, OR 0.2, 0.10–0.055; 95% CI). Administration of clopidogrel over 30 days did not have a significant effect on symptom recurrence in multivariate analysis. Symptom recurrence was significantly increased by radial artery use (p = 0.08, OR 3.9, 1.64–9.39; 95% CI) and COPD (p < 0.0001, OR 6.7, 3.59–12.79; 95% CI) and marginally increased with age (p = 0.04, OR 0.9, 0.94–0.99; 95% CI). Postoperative follow-up time period was not a significant determinant of symptom recurrence in the multivariate analysis.

Postoperative clopidogrel independently decreased adverse cardiac events (p < 0.0001, OR 0.2, 0.10–0.45; 95% CI). Although long-term clopidogrel use appeared to decrease adverse cardiac events in the univariate analysis, it did not reach statistical significance in the multivariate analysis. Adverse cardiac events were independently increased by radial artery use (p < 0.009, OR 2.9, 1.37–6.36; 95% CI), continued tobacco use (p < 0.0001, OR 4.2, 1.93–9.23; 95% CI), COPD (p < 0.0001, OR 3.3, 1.75–6.40; 95% CI), low left ventricular ejection fraction (p < 0.001, OR 4.0, 2.22–7.19; 95% CI), and marginally with diabetes (p = 0.05, OR 1.8, 1.02–3.33; 95% CI) in multivariate analysis. Length of postoperative follow-up period was not a predictor of adverse cardiac events.

Overall mortality was increased with radial artery use, continued smoking, peripheral vascular disease, and poor left ventricular function in the univariate analysis; however, none of these factors reached statistical significance in the multivariate analysis. Again, postoperative clopidogrel use

did not have any affect on overall mortality. Follow-up period did not appear as one of the predictors of mortality.

We then evaluated the effect of clopidogrel on individual end points (Table 3). Clopidogrel receivers had significantly less angina recurrence, myocardial infarction, coronary reintervention, and death compared to non-receivers.

Comparison of individual end points among the short-term and long-term clopidogrel receivers showed that there was no difference between the groups (Table 4).

Survival curves were constructed comparing clopidogrel receivers and non-receivers with respect to the symptom recurrence (Fig. 1), adverse cardiac events (Fig. 2), and overall mortality (Fig. 3). There was a survival benefit for symptom recurrence \((p = 0.0001)\), adverse cardiac events...
of patients with coronary ischemic events [15]. On the basis of these studies, ACC/AHA American Heart Association now recommends clopidogrel to be started upon admission and continued for 9 months after the discharge of patients with acute coronary syndromes [16].

Further evidence for the use of clopidogrel comes from the evidence that ADP is an important mediator of platelet aggregation in endothelium-injured coronary arteries, and combined inhibition of both thromboxane A2 and ADP provides marked protection against platelet aggregation [17]. Therefore, we established a combined regimen with clopidogrel and aspirin following OPCAB to maximize antiplatelet activity.

Since the effect of preoperative aspirin on early graft patency has been shown previously [18], we did not stop aspirin in the preoperative period. Rather aspirin was started before surgery if the patient was not already receiving this medication. Clopidogrel at doses of 0.2 mg/kg combined with aspirin is known to have maximal interruption of graft thrombosis with prolongation of bleeding time in experimental studies [6]. Clopidogrel in higher doses only prolongs bleeding time without further decrease in platelet deposition [6]. Therefore, a combination of clopidogrel 75 mg daily with aspirin 81 mg daily was used during the study.

We did not administer a preoperative clopidogrel loading dose due to obvious concerns over excessive bleeding. Various studies have shown that clopidogrel exposure within 5 days prior to CABG is associated with excessive postoperative blood loss, blood product transfusion, and reexploration for bleeding [19]. ACC/AHA recommendation is to stop clopidogrel at least 5 days prior to elective CABG surgery [20].

The duration of clopidogrel administration was decided according to the original studies done on aspirin and saphenous vein graft patency. It is known that there is a 15–20% attrition rate for saphenous vein grafts in the first year after CABG and 2–4% per year afterward [21]. Since the majority of early graft closures occur in the first postoperative month [18], treatment was continued for 30 days in our earlier experience. However, we continued the drug indefinitely after the CAPRIE study results [3], which showed that patients with prior cardiac surgery had decreased rates of MI, stroke, and rehospitalization with long-term clopidogrel. Our results did not show any benefit of long-term clopidogrel compared to just 30 days with respect to the defined end points. This might be due to the smaller sample size as well as small number of overall adverse events in the study population. We do continue to administer daily clopidogrel (75 mg) and aspirin (81 mg) indefinitely in all patients with OPCAB until there are more data available in this issue.

The association of lower symptom recurrence and adverse cardiac events as well as mortality in this study may be due to the improved graft patency with clopidogrel. Early graft closure is an important issue after OPCAB surgery. Although an increased incidence of thrombotic events was reported after OPCAB [22], others did not find a difference in the hypercoagulability between on-pump CABG and OPCAB [23]. Recently, an increase in platelet activation was reported after OPCAB [24]. It is well known that early graft occlusion after bypass surgery is the result of platelet thrombus due to endothelial damage and altered flow conditions in the bypass conduit. Clopidogrel may act synergistically with aspirin to decrease the abnormal platelet activation and prevent platelet aggregation and early platelet thrombus in the bypass grafts. This might have contributed the improved results associated with clopidogrel administration.

Although increased bleeding complication would be a concern with the addition of clopidogrel, this was not the case in our patient population. Aspirin dose was reduced to 81 mg daily when clopidogrel was added in accordance with CURE trial where the incidence of bleeding complications was dictated mainly by dose of aspirin [25]. There was no difference in the incidence of minor or major bleeding complications in patients receiving postoperative clopidogrel during follow-up.

In summary, the combination of clopidogrel with aspirin after OPCAB resulted in less symptom recurrence, adverse cardiac events, and mortality in our patient population. Although clopidogrel administration beyond 30 days did not improve the outcomes further, this might be due to the small sample size and small number of adverse events during follow-up. Dual antiplatelet therapy with clopidogrel and aspirin did not increase bleeding complications when compared to aspirin.

References


Appendix A. Conference discussion

Dr A. Zlotnick (Haifa, Israel): If I understood right, the group that got clopidogrel was the later group, which means you were more experienced surgeons in OPCAB. Could this be influencing your results?

Dr Gurbuz: We thought about that, too. However, we didn’t change our technique, and there was really no difference in the incidence of adverse events or symptom recurrence between our earlier and later patient groups. So, the answer to your question is “I don’t think so”. And yes, we also thought about it.

Dr A. Al-Aulaqi (Abu Dhabi, United Arab Emirates): I noticed that the p-value was significant only for the use of statins. Were statins only used in the clopidogrel group, or in both groups, and what about the beta blockers and the statins, and what is your protocol for protamine after revascularization, because those are important factors also?

Dr Gurbuz: We started adding statins, again, 6 h after the procedure starting in 2001, and again, since it was a multivariate analysis, statin effect was independent of the clopidogrel effect. The answer to your second question, we do not reverse heparin 100%, we only reverse it about half, and we accept ACTs in 180–190 s.

Dr A. Kappetein (Rotterdam, The Netherlands): Two comments: First one, clopidogrel is not reimbursed in many countries for the indication you describe. If the effect is so strong we should possibly redesign the SYNTAX study to improve the outcomes in the bypass arm.