Dipyridamole Therapy Improves Long-Term Survival After Complete Revascularization in Patients With Impaired Cardiac Function

— A Propensity Analysis —

Eiji Ikeda; Takatoshi Kasai*; Kan Kajimoto; Katsumi Miyauchi*; Naoyumi Kubota*; Takeshi Kurata*; Atsushi Amano; Hiroyuki Daida*

Background Although dipyridamole is no longer used as a mainstream medication for coronary artery disease because of the coronary steal phenomenon, recent studies have shown that the elevation of serum adenosine levels caused by dipyridamole improves cardiac function in heart failure patients. In the present study it was investigated whether use of dipyridamole at the time of complete revascularization affects long-term mortality in patients with impaired left ventricular (LV) function.

Methods and Results The 1,836 consecutive patients who underwent complete revascularization between 1984 and 1992 were assessed; 254 patients with impaired LV function (ejection fraction <50%) were enrolled. Cox proportional hazards regression adjusted for baseline covariates and the propensity score were used to compare the risks for mortality between patients who did and did not take dipyridamole. The mean follow-up period was 12 years; 178 patients (70.1%) took dipyridamole and there were 66 (37.1%) all-cause and 22 (12.4%) cardiac deaths in that group. In the multivariate analysis, the dipyridamole group had a lower risk for both all-cause (hazard ratio (HR) 0.54; p=0.005) and cardiac mortality (HR 0.42; p=0.010).

Conclusion The use of dipyridamole reduced both all-cause and cardiac mortality in patients with impaired LV function. (Circ J 2008; 72: 1588–1593)

Key Words: Adenosine; Coronary artery bypass graft; Mortality; Percutaneous coronary intervention

Dipyridamole is an antiplatelet agent that inhibits the cellular reuptake of adenosine, leading to increased extracellular concentrations of adenosine! Adenosine has cardioprotective actions: it activates adenosine receptors, resulting in attenuation of catecholamine release, β-adrenoceptor-mediated myocardial hypercontraction, and Ca2+ overload via A1 receptors, and increases coronary blood flow and inhibits platelet and leukocyte activation via A2 receptors. A meta-analysis of 13 randomized, placebo-controlled trials published between 1960 and 1992 demonstrated the beneficial effect of dipyridamole with respect to the prevention of angina pectoris, particularly with a longer duration of treatment2 In experimental studies, absolute coronary flow is increased when collateral circulation is not present! However, dipyridamole induced myocardial ischemia that depended on collateral circulation in some patients with coronary artery disease (CAD), because dipyridamole decreased flow to collateral-dependent vascular beds through “coronary steal”4,6. Coronary steal is conventionally defined as an absolute decrease in perfusion, compared with resting flow, to collateralized myocardium following coronary vasodilation. Therefore, dipyridamole and adenosine are used in diagnostic examinations for detecting myocardial ischemia7,8 rather than as treatment for CAD2 because of the coronary steal phenomenon. In recent studies, elevation of serum adenosine by administration of dipyridamole improved cardiac function in patients with heart failure; however, there are few data regarding the long-term effects of dipyridamole on mortality and cardiovascular events in Japanese patients. The aim of this study was to assess whether the use of dipyridamole after complete revascularization affects long-term mortality in patients with impaired left ventricular (LV) systolic function.

Methods

Subjects Data from consecutive patients who had undergone surgical and/or percutaneous coronary revascularization at Juntendo University Hospital between January 1984 and December 1992 were analyzed. Patients were enrolled who met the inclusion criteria: (1) achieved complete revascularization, defined as no un-bypassed major vessels with a ≥50% stenosis12,13 and (2) had impaired LV systolic function, defined as a LV ejection fraction (LVEF) ≤50% on echocardiography at the time when complete revascularization was achieved. Patients who had other known life-threatening diseases at baseline and patients who had associated complex cardiac procedures, such as valve replacement or aneurysm repair at the time of surgical revascularization, were excluded.
Demographic data, including age, gender, and body mass index (BMI), coronary risk factors (blood pressure, lipid profile, fasting plasma glucose, smoking status, family history of CAD), medication use, procedure-related factors, comorbidities (prior myocardial infarction, renal insufficiency, and atrial fibrillation) were prospectively collected in the database at our institution.

For all analyses, patients were divided into 2 groups according to dipyridamole use at the time of complete revascularization. Each patient was further categorized according to the presence of coronary risk factors using the following criteria during the study period: diabetes mellitus was defined as fasting blood glucose ≥140 mg/dl or treatment with oral hypoglycemic drugs or insulin injection; hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or treatment with antihypertensive medications; dyslipidemia was defined as total cholesterol ≥220 mg/dl or high-density lipoprotein-cholesterol <40 mg/dl or triglyceride ≥150 mg/dl or treatment with statins. Renal insufficiency was defined as an estimated creatinine clearance (calculated using the Cockcroft-Gault formula) <30 ml/min or on dialysis. A current smoker was defined as someone who smoked at the time of complete revascularization or who had quit smoking within 1 year before complete revascularization. Patients with isolated PCI were those in whom complete revascularization was achieved by PCI without any bypass grafting.

This study was performed according to the ethics policies of the institution, and was approved by the internal review board.

Outcomes

Survival data were collected by serial contact (every 5 years) with the patients or their families until September 30, 2000 and from the medical records of patients who had died and of those who continued to be followed at our hospital. Information about the continuation of dipyridamole and the circumstances and date of death was obtained from the families of patients who died at home, and details of the cardiac events or the cause of death were supplied by other hospitals or clinics where patients had been admitted. Mortality data were categorized according to the cause of death, such as death from all causes or cardiac death because of CAD, cardiogenic shock, and sudden death.

Statistical Analysis

Continuous variables are expressed as mean±SD and compared using Student’s t-test or the Mann-Whitney U-test. Categorical data are displayed as frequencies and percentages and compared using the chi-square test or Fisher’s exact test. Cox proportional hazards models were used for survival analyses. To adjust the variables that would have been related to the decision regarding dipyridamole therapy at the time of revascularization, propensity analysis was used. Propensity analysis aims to identify patients with similar probabilities of receiving dipyridamole on the basis of the observed clinical characteristics. Variables included in the stepwise multivariate logistic regression analysis were: age; gender; BMI; diabetes mellitus; hypertension; dyslipidemia; current smoker; family history of CAD; use of insulin, oral hypoglycemic agents, nitrates, nicorandil, β-blockers, angiotensin-converting enzyme inhibitors (ACEI), calcium-channel blockers, statins and other lipid-lowering drugs, aspirin, ticlopidine, and warfarin; comorbidities (renal insufficiency, prior myocardial infarction, and atrial fibrillation); and procedure-related factors, such as vessel disease, LVEF, presence or absence of a left main trunk lesion, presence or absence of an arterial bypass graft to the left anterior descending, and whether complete revascularization was achieved by isolated PCI. Based on the results of this logistic regression analysis, the propensity score was calculated for each patient; a higher propensity score indicated a higher probability of being allocated to the dipyridamole group in the present study. The propensity scores were entered into the Cox proportional hazards model as a continuous variable, along with baseline covariates that were used in the propensity score model. Adjusted survival curves were generated using this Cox proportional hazards model in conjunction with other described methods. P-values <0.05 were considered significant. All data were analyzed using Dr SPSS II for Windows (SPSS Inc, Chicago, IL, USA).

Results

Baseline Characteristics

Overall, complete revascularization was achieved in 1,836 patients during the study period and of them, 254 (13.8%) had impaired LV systolic function. Baseline characteristics and clinical events during follow-up (mean, 9.5±3.9 years) were collected for all of these patients: 178 (70.1%) received dipyridamole (150 to 300 mg/day, orally) at the time of complete revascularization was achieved. During the total follow-up period, 15 patients (8.4%) in the dipyridamole group stopped dipyridamole therapy, and 16 patients (21.0%) in the no-dipyridamole group started dipyridamole therapy. The baseline characteristics of the patients with and without dipyridamole are shown in Table 1. More cases with 1-vessel disease and isolated PCI were included in the no-dipyridamole group. More patients were given aspirin in the dipyridamole group; however, fewer patients were given nicorandil, ACEIs, ticlopidine, and warfarin (Table 2). There were no significant differences between the 2 groups for any other variable. All patients underwent PCI with balloon angioplasty; no patients had stent implantation.

Adjusted Analyses of Mortality and Cardiovascular Events

In the propensity score analysis, independent variables associated with dipyridamole use at the time when complete revascularization was achieved included: currently taking nicorandil, aspirin, ticlopidine, and warfarin, presence of atrial fibrillation, and complete revascularization achieved by isolated PCI. The adequacy of the propensity score was confirmed because the area under the receiver-operating characteristics curve was 0.75. Patients on dipyridamole therapy had a mean propensity score of 0.56±0.213, whereas patients not on dipyridamole therapy had a mean propensity score of 0.34±0.277. The ability of the propensity score to adjust for baseline covariates of dipyridamole therapy was evaluated by testing for differences in these covariates within quintiles of the propensity score; the values for important variables associated with dipyridamole therapy were found to be not significantly different between the dipyridamole group and the no-dipyridamole group.

Overall, 100 patients died during follow-up; 39 were cardiac deaths. Using the Cox proportional hazards model to adjust for covariates, dipyridamole use at the time of PCI was an independent and significant predictor of long-term survival, both with respect to death from all causes (hazard
ratio (HR) 0.54; 95% confidence interval (CI) 0.35–0.83; p=0.005) and cardiac death (HR 0.42; 95% CI 0.22–0.82; p=0.010) (Table 3). Based on the adjusted survival curve, dipyridamole use at the time when complete revascularization was achieved was significantly associated with a reduction of long-term mortality from all causes and cardiac death (Figs 1,2).

Discussion

Our registry data showed that dipyridamole treatment at the time when complete revascularization was achieved in patients with impaired cardiac function is associated with a reduction in long-term (>10 years) mortality. The immediate and short-term outcomes of complete revascularization with antithrombotic treatment have been investigated in Japanese populations whose cardiovascular mortality and rate of bleeding complications are different from those in Western populations. However, there have been few studies of the impact of dipyridamole treatment on long-term outcome in patients with LV dysfunction.19,20 Though our study is limited by the fact that it was retrospective, involving an observational cohort, propensity analysis was used to adjust for the different backgrounds.21 Thus, our data demon-

Table 1 Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dip (n=178)</th>
<th>No-Dip (n=76)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.5±8.1</td>
<td>60.7±8.3</td>
<td>0.294</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>26 (14.6)</td>
<td>12 (15.8)</td>
<td>0.809</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.1±2.2</td>
<td>23.1±2.6</td>
<td>0.886</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>66 (37.1)</td>
<td>31 (40.8)</td>
<td>0.577</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>109 (61.2)</td>
<td>50 (65.8)</td>
<td>0.492</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>117 (65.7)</td>
<td>57 (75.0)</td>
<td>0.145</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>134 (75.3)</td>
<td>60 (78.9)</td>
<td>0.529</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>60 (33.7)</td>
<td>22 (28.9)</td>
<td>0.457</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>150 (84.3)</td>
<td>56 (73.7)</td>
<td>0.048</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>12 (6.7)</td>
<td>5 (6.6)</td>
<td>0.962</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>40.7±7.6</td>
<td>42.0±6.5</td>
<td>0.183</td>
</tr>
<tr>
<td>LMT lesion, n (%)</td>
<td>16 (9.0)</td>
<td>2 (2.3)</td>
<td>0.071</td>
</tr>
<tr>
<td>Arterial bypass graft to LAD, n (%)</td>
<td>56 (31.5)</td>
<td>20 (26.3)</td>
<td>0.412</td>
</tr>
<tr>
<td>Diseased vessels, n (%)</td>
<td>0.001</td>
<td>1.5-10.5</td>
<td>0.886</td>
</tr>
<tr>
<td>1</td>
<td>10 (5.6)</td>
<td>12 (15.8)</td>
<td>0.294</td>
</tr>
<tr>
<td>2</td>
<td>37 (20.8)</td>
<td>26 (34.2)</td>
<td>0.485</td>
</tr>
<tr>
<td>3</td>
<td>131 (73.6)</td>
<td>38 (50.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>28 (15.7)</td>
<td>19 (25.0)</td>
<td>0.081</td>
</tr>
<tr>
<td>Renal insufficiency, n (%)</td>
<td>64 (36.0)</td>
<td>23 (30.2)</td>
<td>0.381</td>
</tr>
<tr>
<td>Isolated PCI, n (%)</td>
<td>14 (7.9)</td>
<td>20 (16.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Dip, dipyridamole; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; LMT, left main trunk; LAD, left anterior descending; PCI, percutaneous coronary intervention.

Table 2 Medication Use

<table>
<thead>
<tr>
<th></th>
<th>Dip (n=178)</th>
<th>No-Dip (n=76)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, n (%)</td>
<td>16 (9.0)</td>
<td>7 (9.2)</td>
<td>0.955</td>
</tr>
<tr>
<td>OHA, n (%)</td>
<td>16 (9.0)</td>
<td>9 (11.8)</td>
<td>0.485</td>
</tr>
<tr>
<td>Nitrates, n (%)</td>
<td>162 (91.0)</td>
<td>68 (89.5)</td>
<td>0.701</td>
</tr>
<tr>
<td>Nicorandil, n (%)</td>
<td>27 (15.2)</td>
<td>57 (75.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>ACEI, n (%)</td>
<td>4 (2.3)</td>
<td>8 (10.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>CCB, n (%)</td>
<td>31 (17.4)</td>
<td>15 (19.7)</td>
<td>0.660</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>37 (20.8)</td>
<td>21 (27.6)</td>
<td>0.254</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>16 (9.0)</td>
<td>9 (11.8)</td>
<td>0.485</td>
</tr>
<tr>
<td>Other lipid lowering, n (%)</td>
<td>12 (6.7)</td>
<td>5 (6.6)</td>
<td>0.962</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>150 (84.3)</td>
<td>33 (43.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ticlopidine, n (%)</td>
<td>2 (1.1)</td>
<td>16 (21.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Warfarin, n (%)</td>
<td>26 (14.6)</td>
<td>26 (34.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

OHA, oral hypoglycemic agent; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium-channel blocker. Other abbreviation see in Table 1.

Table 3 Adjusted HR of Dip Use for All-Cause and Cardiac Mortality

<table>
<thead>
<tr>
<th></th>
<th>All-cause death</th>
<th>Cardiac death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR</td>
</tr>
<tr>
<td>No-dip</td>
<td>34/76</td>
<td>1.00</td>
</tr>
<tr>
<td>Dip</td>
<td>66/178</td>
<td>0.54</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval. Other abbreviation see in Table 1. The propensity score was entered into this Cox proportional hazards model as a continuous variable, along with the baseline covariates that were used in the propensity score model.
Dipyridamole and Survival

Circulation Journal   Vol.72, October 2008

strated that dipyridamole therapy was effective in terms of
terminal clinical outcomes in Japanese patients in whom
complete revascularization was achieved.

Schwartz et al described the benefits of dipyridamole
treatment in PCI patients.22 In an early study of 376 patients
undergoing angioplasty and randomized to receive either
dipyridamole (225 mg daily) and aspirin (990 mg) or place-
bo for 4–7 months after angioplasty, they reported that
there was a reduction in periprocedural Q-wave myocardial
infarction when antiplatelet therapy was started before the
procedure (6.9% vs 1.6%; p=0.011). Furthermore, experi-
mental studies support the concept that vasodilators may
reduce ischemia by increasing collateral blood flow to
ischemic myocardium.23,24

However, Tran and Anand stated that the use of dipyri-
damole in patients with CAD was not recommended in their
report, which summarized the current state of evidence
regarding antiplatelet treatment in patients with CAD.25

They identified 47 trials (n=59,821) between 1960 and 2004
and concluded that current clinical trial evidence favors the
use of aspirin or clopidogrel, not dipyridamole, as the first-
line agent for patients with CAD. In addition, Dieker et al
reported that the combination of aspirin and dipyridamole
failed to regress coronary atherosclerosis in patients with
CAD.26 They performed quantitative coronary angiography
of non-infarcted arteries on paired cine-angiograms of 149
patients from fibrinolytic trials, who were randomized to
either continue the daily combination of 50 mg aspirin and
400 mg dipyridamole or to matching placebo. There was no
difference between the groups in the angiographic parame-
ters: changes in minimal luminal diameter and diameter
stenosis. Considering those results, it is still unclear and
controversial whether dipyridamole has beneficial effects
for patients with CAD.

On the other hand, focusing on the effect of dipyridamole
for patients with heart failure, Sanada et al suggested that

Fig 1. Adjusted survival curves (all-cause
death) of patients with and without dipyrida-
mole therapy. A statistically significant differ-
ence was observed between patients taking
dipyridamole and patients not taking dipyrida-
mole at the time when complete revasculariza-
tion was achieved.

Fig 2. Adjusted survival curves (cardiac death)
of patients with and without dipyridamole ther-
apy. A statistically significant difference was
observed between patients taking dipyridamole
and patients not taking dipyridamole at the time
when complete revascularization was achieved.
additional administration of dipyridamole improved the pathophysiology of heart failure in a prospective, open, randomized study.27 They enrolled 28 patients attending specialized heart failure outpatient clinics, who were then randomized into 3 groups with or without dipyridamole (Control: n=9; 75 mg/day: n=9; 300 mg/day: n=10), in addition to their original medications, and followed up for 1 year. Although the baseline conditions were comparable, the researchers found that chronic dipyridamole treatment improved coronary flow reserve and LV systolic function in ischemic cardiomyopathy patients.28 Six outpatients with CAD and LVEF <40% were treated with dipyridamole 200 mg twice daily for 6 months. Myocardial function and perfusion were measured using velocity-encoded cine magnetic resonance stress perfusion. Although there was no change in New York Heart Association functional and angina classes at 6 months, the LVEF, hyperemic coronary sinus flow, and stress-induced relative myocardial perfusion increased. The results of those studies are similar to those of our study. All report that dipyridamole is associated with better outcomes, and our study extends the benefit of dipyridamole to a clinical hard endpoint. Previous trials provide surrogate endpoints, such as myocardial function and perfusion, whereas our study demonstrates mortality reduction for the most important cardiovascular endpoints. In addition, as compared with the other studies that showed no clinical benefit of dipyridamole in patients with CAD, a lower dose of dipyridamole was administered. Such differences in the dosage might affect the differences in outcomes.

Both direct and indirect effects of dipyridamole on the heart could theoretically account for improved collateral flow. Direct dilatation of collateral channels has been demonstrated in other studies, but a reduction in LV filling could also improve collateral flow indirectly by decreasing the compressive forces on collateral vessels.30 Under certain conditions, however, vasodilators may have adverse effects on collateral flow. Vasodilator-induced hypotension is generally beneficial because of the associated decrease in LV wall tension, but an excessive reduction in perfusion pressure may be harmful.31 Vasodilators may decrease flow to an ischemic region by markedly increasing flow to surrounding nonischemic areas. This diversion of flow from ischemic to nonischemic tissue has been termed myocardial steal or coronary steal.32 However, after complete revascularization, coronary steal did not happen and therefore our study, which only enrolled patients who had undergone complete coronary revascularization, has significant value.

Study Limitations
This was a single center, observational study of daily clinical practice that involved retrospective data collection. Although propensity analyses are powerful,33 they are inherently limited by the number and accuracy of the variables evaluated. Therefore, further investigation is needed to evaluate data from other institutions.

Conclusion
In a retrospective study involving consecutive revascularization patients with impaired LV function, we demonstrated that the use of dipyridamole significantly reduced long-term all-cause and cardiovascular mortality (>10 years) after revascularization.

References

Circulation Journal Vol.72, October 2008


