

Routine functional testing after percutaneous coronary intervention: results of the Aggressive Diagnosis of Restenosis in High-Risk Patients (ADORE II) trial

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Background — It is unclear whether routine or selective functional testing is optimal following percutaneous coronary intervention (PCI) in high-risk patients.

Objectives — The aim of this trial was to compare exercise endurance, functional status, and quality of life (QOL) among high-risk patients randomized to either routine or selective functional testing following PCI.

Methods — We randomized 84 patients to either routine or selective functional testing. Patients had one or more of the following: multivessel PCI, diabetes mellitus, left ventricular ejection fraction $\leq 35\%$, and/or PCI of the proximal left anterior descending artery. Patients in the routine arm ($n = 41$) underwent maximum endurance exercise treadmill testing (ETT) with nuclear perfusion imaging at 1.5 and 6 months. Patients in the selective arm ($n = 43$) only underwent functional testing for a clinical indication. All patients underwent a maximum endurance ETT at 9 months. Exercise endurance, functional status, and QOL were assessed at 9 months.

Results — Most patients were middle-aged men (58 ± 10 years old; 87% male) who underwent PCI with stenting (94%). Among routine functional testing patients, 27.0% and 41.9% had a positive functional test at 1.5 and 6 months, respectively. Exercise endurance was improved in the routine vs. selective arm at 9 months (metabolic equivalents: 10.3 ± 2.6 vs. 8.6 ± 3.0 , $P = 0.013$). There was no difference in improvement from baseline for the Duke Activity Status Index, the Seattle Angina Questionnaire, or the SF-36. Nine-month cumulative incidences of cardiac procedures and clinical events were not significantly different.

Conclusions — Routine functional testing following PCI in high-risk patients may lead to improved exercise endurance but not improved QOL.

Keywords: PCI – angioplasty – restenosis – functional testing – stress testing – high-risk patients.

Introduction

More than 800,000 percutaneous coronary interventions (PCIs) are performed annually in North America¹⁻³. For patients undergoing balloon angioplasty, restenosis rates are 30-40%⁴. For patients under-

going stent implantation with bare metal stents, restenosis rates are 20-30%⁴. Implantation of a drug-eluting stent leads to restenosis rates in the single digits⁵. Because approximately 50% of patients with restenosis remain asymptomatic⁶, many physicians still employ a strategy of routine functional testing after PCI, in which all patients undergo functional testing⁷⁻⁹. In contrast, other physicians use a selective or clinically driven strategy, in which patients do not undergo functional testing unless they develop recurrent symptoms. It remains unclear which functional testing strategy is optimal for patients after PCI: an aggressive strategy of routine testing or a conservative strategy of selective testing.

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According to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, routine functional testing post-PCI should not be performed¹⁰. In the ADORE trial, we randomized patients to routine versus selective functional testing, and found that routine functional testing post-PCI confers no additional benefit to the general patient population¹¹. However, the ACC/AHA guidelines suggest that routine functional testing may be advantageous in selected groups of high-risk patients, including those with multi-vessel PCI, diabetes mellitus, left ventricular ejection fraction (LVEF) $\leq 35\%$ and/or PCI of the proximal left anterior descending coronary artery (LAD). For this reason, we performed the ADORE II trial to directly compare routine versus selective functional testing strategies in a randomized group of high-risk patients. The objective of this trial was to determine whether routine functional testing confers any benefit to high-risk patients with respect to functional status and quality of life.

Methods

PATIENTS

The methods employed in the ADORE II trial are similar to those used in the ADORE trial¹¹. In the ADORE II trial, a total of 84 high-risk patients were randomized to either routine ($n = 41$) or selective ($n = 43$) functional testing following PCI. Patients were eligible for participation if they had undergone complete coronary revascularization by any accepted percutaneous techniques (balloon angioplasty, stenting, atherectomy). Patients randomized had one or more of the following high-risk characteristics: multi-vessel PCI, diabetes mellitus, LVEF $\leq 35\%$ and/or PCI of the proximal LAD. Patients were also required to have undergone complete revascularization, defined as a procedure in which all stenoses $\geq 60\%$ were reduced by at least 20% and had residual stenoses $< 50\%$. Exclusion criteria included inability to give informed consent, uninterpretable baseline ECG, planned functional testing, pregnancy or likely to become pregnant, contraindications for or inability to perform exercise treadmill testing (ETT), contraindication for repeat cardiac procedures, medical condition with a prognosis of ≤ 1 year, unlikely to be available for follow-up functional testing and inability to read or understand either English or French.

RANDOMIZATION

Randomization took place after PCI, but prior to discharge from hospital. Each patient provided written consent before randomization. Internet randomization

was performed at a central location. Blocking by treatment group and stratification based on each of the four high-risk characteristics ensured a similar distribution of patients and high-risk characteristics in each treatment arm. The Ethics Committee approval was obtained at each of the participating centres.

STUDY PROTOCOL

At the time of randomization, baseline procedural and clinical characteristics were collected. Procedural characteristics included number, type and location of all lesions, type of procedure, devices used, and pre- and post-procedure stenosis. Clinical characteristics included demographics, presence of co-morbidities, prior procedures and medical therapy. At baseline, patients answered questionnaires in order to assess their functional status and quality of life at baseline. The following questionnaires were used: Duke Activity Status Index (DASI)¹², the Seattle Angina Questionnaire (SAQ)¹³, and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)¹⁴. The DASI assesses the patients' ability to perform a range of activities, such as walking up stairs and doing light housework. The SAQ assesses the quality of life of patients with coronary artery disease in five categories: physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception. The SF-36 measures the general health status of the patient in eight dimensions: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health.

Patients randomized to routine functional testing underwent a maximum endurance ETT with nuclear perfusion imaging at 1.5 and 6 months. Patients randomized to the selective arm were limited to functional tests for clinical indications. At 9 months, all patients underwent a maximum endurance Modified Bruce ETT and filled out the DASI, SAQ and SF-36 questionnaires. All ECGs and nuclear perfusion tests were assessed by the treating physician at the study centre, and the results were forwarded to the coordinating centre. Additional clinical data, including the use of medical therapy, was also collected.

END POINTS

All end points were assessed at 9 months. The primary end point of functional status was assessed by maximal exercise endurance on a treadmill (measured as Metabolic Equivalents [METS]). Secondary end points included functional status results from the DASI questionnaire and quality of life results from the SAQ and SF-36 questionnaires. Improvements in functional

status and quality of life were measured by subtracting the baseline questionnaire scores from the 9-month questionnaire scores. Although the ADORE II trial was not powered to examine repeat cardiac procedures (cardiac catheterization, repeat PCI and coronary artery bypass graft (CABG) surgery) or clinical events (unstable angina, myocardial infarction (MI), and death), these events were nonetheless tabulated. End points were evaluated by the End Points Committee, whose members were blinded to the treatment course of all patients. Adverse clinical events were also evaluated by the End Points Committee.

STATISTICAL ANALYSIS

Continuous data are presented as the mean \pm standard deviation and were compared with a Student's unpaired t-test. Dichotomous data are presented as percentages and were compared using a Chi square test. Event-free survival in the two arms was examined using a cumulative incidence Kaplan-Meier curve, and differences between the two treatment arms were evaluated using the log-rank test. Data were analysed according to the intention-to-treat principle. A *P*-value ≤ 0.05 was considered to be statistically significant.

Results

BASELINE CHARACTERISTICS

The routine and selective functional testing groups had similar baseline characteristics (table 1). A total of 40% of patients had two or more high-risk characteristics. Due to the use of stratification during randomization, the proportions of each type of high-risk characteristic were evenly distributed between the two treatment arms. Most patients were middle-aged men (58 ± 10 y, 87% male) who underwent PCI with stent deployment (94%). A total of 24% of patients had prior MI's, 23% had prior revascularization procedures and 43% received glycoprotein IIb/IIIa inhibitors at the time of PCI. Lesion location, lesion complexity, and lesion severity were well balanced between the two groups.

FUNCTIONAL TESTING

There was a five-fold difference in the rates of functional testing between the routine and selective functional testing arms (84% vs. 16%, respectively). Only one off-protocol test occurred in the routine arm, while 13 off-protocol tests occurred in the selective arm. In the routine functional testing arm, 21.6% of patients had a positive treadmill test and 5.6% had moderate

to large reversible imaging defects at 6 weeks. At 6 months, 38.7% had a positive treadmill test and 22.6% had moderate to large reversible imaging defects (table 2). A total of 27.0% and 41.9% of patients had positive functional tests by either the treadmill or nuclear component at 6 weeks and 6 months, respectively. Of the patients with positive treadmill and/or nuclear tests at 6 weeks, 45% also had positive treadmill and/or nuclear tests at 6 months. Of the 54.5% of patients with positive treadmill and/or nuclear tests at 6 weeks or 6 months, 11% developed clinical events and 22% had further cardiac procedures.

PRIMARY AND SECONDARY END POINTS

For the primary end point, patients in the routine arm had significantly improved maximal exercise endurance compared to patients in the selective arms (10.3 ± 2.6 METS vs. 8.6 ± 3.0 METS, *P* = 0.013) (table 3). There was also a significantly greater number of patients in the routine arm who were able to achieve $\geq 85\%$ of their maximum predicted heart rate achieved (MPHR) (54.5% vs. 27.0%, *P* = 0.019). There was a trend for better mean % MPHR in the routine arm (84.5 ± 17.4 vs. 77.0 ± 14.1 , *P* = 0.051). The frequency of electrically or clinically positive functional tests showed no significant differences between the two treatment groups (table 3).

There were no significant differences between the two treatment arms in any of the secondary end points of the trial. Although anginal stability, frequency, disease perception and role physical all improved, demonstrating the utility of PCI, improvements were similar in the two groups. The DASI measure of functional status was comparable between the two groups. Similarly, there were no significant differences in quality of life, evaluated by the five subscales of the SAQ and the eight subscales of the SF-36 (table 4).

In both groups, repeat angiograms were the predominant cardiac procedure (18.1% vs. 21.6%, *P* = 0.72) (table 5). Small numbers of repeat PCI's (9.1% vs. 8.1%, *P* = 0.88), and CABG's (3.0% vs. 2.7%, *P* = 0.93) were performed in both treatment arms. The majority of clinical events were due to hospitalizations for unstable angina (15.1% vs. 21.6%, *P* = 0.34) (table 5). The number of MIs (3.1% vs. 5.4%, *P* = 0.64) and deaths (3.0% vs. 0%, *P* = 0.29) in both the routine and selective patient groups was small.

Discussion

The ADORE II trial was designed to examine functional status and quality of life among high-risk patients randomized to routine versus selective functional testing following PCI. Several studies to date

Table 1. – Baseline clinical and procedural characteristics

| | Functional testing strategy | |
|--|-----------------------------|-----------------------|
| | Routine (n = 41) | Selective (n = 43) |
| Clinical characteristics (%) | | |
| Male | 90.2 | 83.7 |
| Age (y), mean \pm SD [†] | 57.0 \pm 9.7 | 59.3 \pm 10.4 |
| CCS* angina class (pre PCI [‡]) III-IV | 31.7 | 30.2 |
| Hyperlipidaemia | 61.0 | 76.2 |
| Prior MI [‡] | 24.4 | 23.3 |
| Prior PCI | 19.5 | 18.6 |
| Prior CABG [‡] | 2.4 | 4.7 |
| High-risk characteristics (%) | | |
| Multi-vessel PCI | 43.9 | 48.8 |
| Diabetes mellitus | 34.1 | 34.9 |
| Left ventricular ejection fraction \leq 35% | 19.4 | 16.7 |
| PCI of the proximal LAD [§] | 17.4 | 17.1 |
| Procedural characteristics (%) | | |
| Stent | 92.7 | 95.3 |
| GP [¶] IIb/IIIa inhibitor | 46.3 | 39.5 |
| Lesion location | | |
| LAD | 45.4 | 48.8 |
| Cx [¶] | 28.0 | 25.6 |
| RCA [‡] | 25.3 | 23.2 |
| Other | 1.3 | 2.4 |
| ACC/AHA [¶] class B2 or C | 79.3 | 85.3 |
| Stenosis mean \pm SD | | |
| Pre-PCI | 82.7 \pm 68.6 | 85.7 \pm 74.9 |
| Post-PCI | 1.8 \pm 6.79 | 3.0 \pm 5.7 |

[†]Standard deviation; *Canadian Cardiovascular Society; [‡]Percutaneous coronary intervention; [‡]Myocardial infarction; [¶]Coronary artery bypass graft surgery; [§]Left anterior descending coronary artery; [¶]Glycoprotein; [¶]Circumflex; [‡]Right coronary artery; [¶]American College of Cardiology/American Heart Association.

Table 2. – Functional test results of patients undergoing routine functional testing

| | Timing of functional test | |
|--|---------------------------|-----------------|
| | 6 weeks | 6 months |
| Number of METS [‡] achieved (mean \pm SD [†]) | 7.9 \pm 2.6 | 9.7 \pm 2.8 |
| MPHR [‡] \geq 85% (% of all patients) | 46.0 | 54.8 |
| Mean % MPHR [‡] achieved (mean \pm SD [†]) | 81.0 \pm 11.8 | 86.3 \pm 11.5 |
| Electrically and/or clinically positive [‡] (% of all patients) | 21.6 | 38.7 |
| Imaging positive (% of all patients) | 5.6 | 22.6 |
| Electrically, clinically or imaging positive (% of all patients) | 27.0 | 41.9 |
| Electrically and clinically negative (% of all patients) | 59.5 | 48.4 |

[‡]Metabolic equivalents; [†]Standard deviation; [‡]Maximum predicted heart rate; [‡]Imaging was considered positive if there was a moderate or large area of reversible ischaemia.

Table 3. – Functional test results at 9 months

| | Functional testing strategy | | P-value |
|--|-----------------------------|-----------------|---------|
| | Routine | Selective | |
| Number of METS [‡] achieved (mean \pm SD [†]) | 10.3 \pm 2.6 | 8.6 \pm 3.0 | 0.01 |
| MPHR [‡] \geq 85% (% of all patients) | 54.5 | 27.0 | 0.02 |
| Mean % MPHR [‡] achieved (mean \pm SD [†]) | 84.5 \pm 17.4 | 77.0 \pm 14.1 | 0.05 |
| Electrically and/or clinically positive (% of all patients) | 21.2 | 21.6 | 0.97 |
| Electrically and clinically negative (% of all patients) | 75.7 | 70.3 | 0.61 |

[‡]Metabolic equivalents; [†]Standard deviation; [‡]Maximum predicted heart rate.

Table 4. – Functional status and quality of life comparison between baseline and 9 months^δ

| | Functional testing strategy | | P-value |
|--|-----------------------------|-------------|---------|
| | Routine | Selective | |
| Duke Activity Status Index† (mean ± SD)* | 6.7 ± 15.5 | 8.8 ± 18.7 | 0.61 |
| Seattle Angina Questionnaire‡ (mean ± SD) | | | |
| Exertional capacity | 8.9 ± 17.4 | 6.8 ± 28.0 | 0.69 |
| Anginal stability | 48.8 ± 30.1 | 37.5 ± 42.6 | 0.31 |
| Anginal frequency | 18.0 ± 23.7 | 18.6 ± 30.4 | 0.93 |
| Treatment satisfaction | 10.1 ± 29.7 | 11.3 ± 33.6 | 0.89 |
| Disease perception | 27.6 ± 22.9 | 25.5 ± 26.9 | 0.65 |
| Medical Outcomes Study 36-Item Short-Form Health Survey¥ (mean ± SD) | | | |
| Bodily pain | -1.6 ± 29.6 | 4.2 ± 33.2 | 0.43 |
| General health | 3.1 ± 14.8 | 4.6 ± 14.4 | 0.68 |
| Physical functioning | 2.9 ± 30.7 | 8.3 ± 39.8 | 0.51 |
| Role physical | 22.1 ± 42.5 | 25.7 ± 57.3 | 0.77 |
| Vitality | 7.6 ± 22.2 | 10.6 ± 30.0 | 0.63 |
| Social functioning | 2.7 ± 21.8 | 3.0 ± 32.3 | 0.96 |
| Role-emotional | 2.0 ± 61.4 | 17.9 ± 87.8 | 0.38 |
| Mental health | 4.3 ± 21.2 | 0.0 ± 19.1 | 0.36 |

δ Improvement in functional status and quality of life were measured by subtracting baseline scores from 9-month scores.

† The range of scores is 0 to 58.2, with higher scores indicating better functional status.

‡ The range of scores is 0 to 100, with higher scores indicating better quality of life.

¥ The range of scores is 0 to 100, with higher scores indicating better health status.

* Standard deviation.

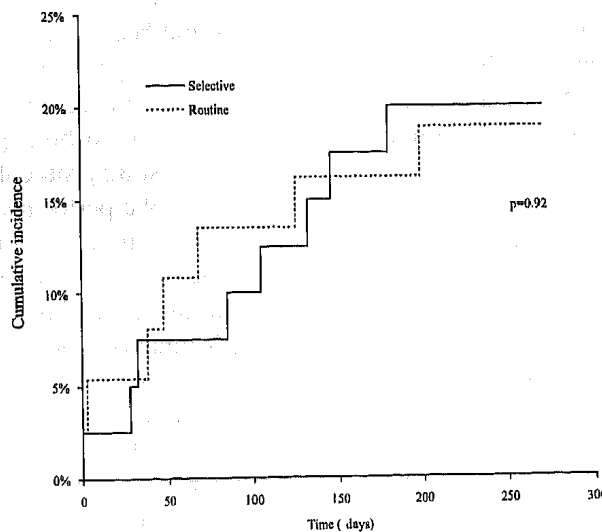


Fig. 1. – Cumulative incidence rate of composite cardiac procedures.

Table 5. – Clinical events and cardiac procedures at 9 months.

| | Functional testing strategy | | P-value |
|-------------------------|-----------------------------|-----------|---------|
| | Routine | Selective | |
| Clinical events (%) | | | |
| Cardiac death | 3.0 | 0 | 0.29 |
| Myocardial infarction | 3.0 | 5.4 | 0.64 |
| Unstable angina | 15.1 | 21.6 | 0.35 |
| Clinical procedures (%) | | | |
| Repeat angiogram | 18.2 | 21.6 | 0.72 |
| Repeat PCI | 9.1 | 8.1 | 0.88 |
| Repeat CABG | 3.0 | 2.7 | 0.93 |

have demonstrated that although PCI has little impact on clinical event rates, it may lead to major improvement in functional status and quality of life^{11,15-16}. However, the ADORE II study is the first to assess whether an aggressive strategy of routine functional testing post-PCI leads to a greater improvement in functional status and/or quality of life in high-risk patients than a selective strategy of functional testing.

We found that patients randomized to the routine functional testing arm exhibited a significant improvement in functional status, measured by METS, when compared to patients in the selective functional testing arm. The routine arm also had a significantly larger number of patients achieving a MPHR $\geq 85\%$. However, no difference in functional status was detected by the DASI questionnaire. We believe that the observed improvement in functional status in the routine arm may be attributable to a 'training effect', as these patients performed two functional tests prior to their 9-month functional test. Multiple studies have demonstrated that even moderate exercise training in patients with coronary artery disease results in improved exercise capacity and functional status¹⁷⁻¹⁸. Our results suggest that even minor exposure to exercise treadmill testing may confer some benefit to functional status in high-risk patients. Alternatively, the 6-week and 6-month functional tests may serve to reassure both the patient and the clinician that the patient can exercise safely. This may increase the patients' willingness to exercise to their maximum capacity during the 9-month test.

Routine functional testing is often criticized for leading to unnecessary procedures. Despite the five-fold increase in functional testing rates in the routine arm, our study did not demonstrate a greater number of cardiac procedures in this group. While there was no significant reduction in clinical events in the routine arm, our results had limited power to detect such differences due to the small sample size of our trial. A larger trial might reveal that this difference in clinical events is significant. However, our results imply that routine functional testing provides little benefit for the early detection and/or treatment of restenosis in high-risk patients.

PREVIOUS STUDIES

Routine post-PCI functional testing is still commonly used¹⁹ despite the ACC/AHA guidelines discouraging this practice¹⁰. Additional studies suggest that there is substantial variation in the use of functional testing among centres²⁰. Furthermore, the presence of high-risk characteristics does not appear to affect a physician's decision to employ routine or selective functional testing²⁰. The ADORE trial was the first trial to examine routine versus selective functional testing in the general patient population¹¹. This trial

found that routine functional testing confers no benefit with respect to functional status or quality of life.

However, a number of studies have examined the value of routine functional testing as a means of identifying restenosis²¹⁻²⁴. These studies found that exercise treadmill testing alone is poorly diagnostic of restenosis, with sensitivity and specificity estimated at 46% and 77%, respectively²²⁻²⁴. The addition of nuclear or echocardiographic imaging significantly improves the diagnostic ability (sensitivity and specificity of 87% and 78%, and 63% and 87%, respectively)²⁴. Numerous studies have shown that routine functional testing with an ETT and perfusion imaging can identify patients with restenosis^{21,25}. Still, the clinical value of aggressively attempting to diagnose restenosis is unclear. Due to the increasing use of drug-eluting stents and the consequent reduction in restenosis rates, the diagnostic yield of routine functional testing has been declining²⁴. Consequently, the cost to identify an asymptomatic patient with restenosis has been increasing²⁶.

CHOICE OF END POINTS AND TESTING PROTOCOL

Because clinical events following PCI occur infrequently and because the primary reason for PCI is the treatment of symptoms, we chose to examine functional status and quality of life – end points that are highly relevant to both patients and physicians. We chose our testing protocol on the basis of several considerations. We performed an exercise test at 6 weeks because it is the most common testing strategy used by physicians^{11,15}, it provides important prognostic information²⁷, and because it objectively measures a patient's functional ability. In addition, we employed nuclear perfusion at 6 weeks because of the improved sensitivity and specificity it provides for the diagnosis of restenosis. End points were evaluated at 9 months because physicians needed time to respond to the results of the 6-month functional test – a second exercise-nuclear perfusion scan performed in order to accurately document the incidence of restenosis²⁵. It has been well established that events that occur during the first 6 months post-PCI are usually related to restenosis. Events that occur after the first 6 months are almost always due to new coronary lesions²⁸.

LIMITATIONS

Several potential limitations of our study should be noted. First, our results with respect to clinical events must be interpreted with caution, because the ADORE II trial was neither designed nor powered to examine this issue. Secondly, patients were required to fill out the baseline DASI, SF-36 and SAQ questionnaires following their PCI but prior to hospital

discharge. In order to measure the improvement in quality of life and functional status, patients were asked to fill out the questionnaires with respect to their status during the 4 weeks prior to hospitalization. Therefore, these results could be subject to recall bias. Thirdly, we did not collect data regarding daily physical activity of these patients (e.g., rehabilitation, return to work), which could have impacted on our results. However, our study assigned functional testing strategy randomly, following the patients' index PCI. As a consequence, we would expect an equal balance in the daily physical activity following the patients' PCI between the two treatment arms.

Conclusion

In conclusion, we found a significant improvement in functional status, measured in METS, among high-risk patients undergoing routine functional testing. However, additional results from the DASI measuring functional status detected no significant difference between the two treatment arms. Routine functional testing provides no benefit in the SAQ and SF-36 quality of life measures among high-risk patients. Thus, the ADORE II trial suggests routine functional testing following PCI in high-risk patients may lead to improved exercise endurance but does not lead to improved quality of life.

We also observed similar clinical events and procedure use in the two treatment arms. These results suggest that routine functional testing may provide little benefit for the early detection and treatment of coronary restenosis in this high-risk patient population. However, due to our limited statistical power to examine clinical events and procedure use, these results should be interpreted with caution until they are confirmed in a large, multi-centre clinical trial.

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Appendix

The following investigators and institutions participated in the ADORE II Trial: Steering Committee – M.J. Eisenberg (principal investigator), J. Blankenship, T. Huynh, L. Pilote; Endpoints Committee – N. Racine (Chair), M. Palaic, L. Rudski; Coordinating Center – B. Wilson, F. Teng; Investigators (in order of enrollment) – C. Lauzon: Centre Hospitalier de la Région de l'Amiante, Thetford Mines, Quebec, Canada; T. Huynh: Montreal General Hospital, Montreal, Canada;

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