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Multicentre, open-label, randomised controlled clinical trial to assess the efficacy and safety of appropriate target values for lipid management in patients who have mild-to-moderate stenotic lesions with high-risk plaques in coronary arteries: study protocol

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ABSTRACT

Introduction To detect patients at high risk of developing myocardial infarction, plaque characteristics as well as the degree of stenosis in coronary arteries should be evaluated. However, unstable plaque or severe calcification detected via coronary artery CT (CACT) is not reflected in risk stratification according to current guidelines. It is hypothesised that patients with high-risk findings on CACT (even those without proven history of coronary artery diseases; CAD) should be strictly managed to lower their low-density lipoprotein cholesterol (LDL-C) levels to targets of secondary prevention. Currently, however, there is no evidence based on prospective randomised intervention studies to prove this hypothesis.

Methods and analysis Patients with mild-to-moderate stenotic lesions with positive remodelling or severe calcification, but without any history of CAD, will be randomly allocated to group A (reduce LDL-C to <120~160 mg/dL according to the primary prevention criteria based on the Japan Atherosclerosis Society (JAS) Guideline for Prevention of Atherosclerotic Cardiovascular Diseases 2017) and group B (reduce LDL-C to <70 mg/dL according to the secondary prevention criteria for high risk based on the JAS Guideline). They will be strictly managed to achieve the LDL-C targets. We will follow-up and evaluate the composite endpoints consisting of major cardiovascular events (death from CAD, non-fatal myocardial infarction, operation for coronary revascularisation and stroke) and stenosis progression or new stenosis development for 3 years.

Ethics and dissemination The study was approved by the National Hospital Organization Central Research Ethics Committee. The results of this study are scheduled to be published within 2 years after study completion via conference presentation or journal publication.

Trial registration number UMIN000031136.

Strengths and limitations of this study

► This is the first intervention trial evaluating a prevention strategy in patients with mild-to-moderate stenotic lesions with high-risk characteristics detected on coronary artery computed tomography (CACT), but without proven coronary artery diseases (CAD).

► The primary prevention criteria for reducing low-density lipoprotein cholesterol (LDL-C) to <120~160 mg/dL and secondary prevention criteria for reducing LDL-C to <70 mg/dL will be compared in this trial, even though most previous trials investigating the effects of LDL-C-lowering therapy have compared dose or strength of statins or other medicines.

► Stenosis progression or new stenosis development detected on CACT, as well as major cardiovascular events, are included as constituent endpoints of primary outcome.

► The study will be conducted in Japan and most enrolled subjects will be Japanese hence, this study cannot conclude on the effects of prevention strategy in general populations.

► The study design involves an open-label trial because without knowing the allocated group, participants and care-providers will not be able to achieve the assigned LDL-C target during the trial.

INTRODUCTION

Effective prevention of myocardial infarction is significantly important for prolonging healthy life and suppressing surging medical costs. Myocardial infarction is not necessarily caused by a severe stenotic lesion and is known to be often caused by the rupture of an unstable plaque in a mild-to-moderate stenotic lesion.[1] This implies that, in order to find patients at a high risk of developing myocardial infarction, plaque

characteristics, rather than the degree of stenosis of the coronary artery, should be evaluated.

However, cardiac catheter examination (coronary angiography; CAG), which is considered the gold standard for diagnosis of coronary artery disease (CAD), excels in the evaluation of the degree of stenosis but cannot evaluate plaque characteristics. Therefore, it is necessary to add invasive examinations including intravascular endoscopy, intravascular ultrasound (IVUS) or optical coherence tomography for the evaluation.

Coronary artery CT (CACT) is a non-invasive examination that can be performed on an outpatient basis. It is conducted in more than 400 000 patients annually and its usage is increasing year by year in Japan.[2] Although CACT is inferior to cardiac catheterisation at evaluating stenosis accurately, it is excellent in the evaluation of plaque characteristics on the blood-vessel wall. It has been reported that findings such as a low attenuation plaque, positive remodelling and a napkin-ring sign suggest the presence of unstable plaques[3 4] and the presence of these unstable plaques is associated with a high prevalence of acute coronary syndrome (ACS).[5] In addition, coronary artery calcification score (CACS) obtained from CACT is useful for prognosis; in cases with high values of CACS, it has been reported that death from cardiovascular events, including myocardial infarction, occurs at a high rate.[6]

The Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017[7] recommend lipid management with target low-density lipoprotein cholesterol (LDL-C) levels of less than 100 mg/dL as secondary prevention when there is coronary artery stenosis or a history of myocardial infarction, and strict management targeting LDL-C levels of less than 70 mg/dL is required for pathologies which are at high risk of developing atherosclerotic diseases including ACS. Under similar guidelines in Europe and the USA,[8 9] CAD is classified to be at very high risk and lipid management with target LDL-C levels of less than 70 mg/dL is recommended. However, when patients do not have proven CAD, the presence of unstable plaque or hyper-calcification detected in CACT is not reflected in risk stratification. Therefore, patients with high-risk plaques but without ACS onset are only required to achieve the LDL-C goals for primary prevention according to the current guidelines. Several clinical trials using IVUS have revealed that lowering- LDL-C levels to less than 70 mg/dL was effective for regression of coronary artery plaque volume.[10–12] In particular, the ESTABLISH study demonstrated that strict LDL-C -lowering to 70 mg/dL resulted in a 13.1% reduction in plaque volume in 6 months,[10] which might have led to a significant reduction in cardiovascular events in a follow-up for 4.2 years.[11] In PRECISE-IVUS study, a combination of statins and ezetimibe, which lowered average LDL-C levels to 70 mg/dL, reduced plaque volume more effectively than statins alone.[12] Therefore, in the current study in patients with high-risk plaques detected on CACT but without proven history of CAD,

we will investigate if strict management targeting LDL-C levels of less than 70 mg/dL can prevent cardiovascular events and progression of coronary artery plaques more effectively than standard management of LDL-C for primary prevention.

METHODS/DESIGN
Study design
This is a multicentre, open-label, randomised, controlled, parallel-group clinical study. The complete design of this trial is shown in figure 1.

The following 16 institutions will participate in this study in which the eligibility and outcomes will be judged by experienced specialists for interpretation of CACT: Hokkaido Medical Center, Hakodate National Hospital, Mito Medical Center, Saitama National Hospital, Yokohama Medical Center, Sagamihara National Hospital, Kanazawa Medical Center, Kyoto Medical Center, Osaka National Hospital, Okayama Medical Center, Kure Medical Center, Iwakuni Clinical Center, Kobe Medical Center, Ehime Medical Center, Kyushu Medical Center and Kumamoto Medical Center.

Objective
Primary endpoint
To investigate the efficacy of strict lipid management by secondary prevention high-risk criteria for preventing major cardiovascular events and progression of coronary artery stenosis in study subjects without proven history of CAD who have mild to moderate stenosis with unstable plaques or severe calcification detected by CACT, in comparison with standard lipid management as per the primary prevention criteria.

Major secondary endpoints
To evaluate the safety and efficacy in preventing each component of primary endpoints by strict lipid management with secondary prevention high-risk criteria in study subjects without proven history of CAD who have mild-to-moderate stenosis with unstable plaques or severe calcification detected by CACT, in comparison with standard lipid management as per primary prevention criteria.

After randomization of the participants into group A or B, they will be treated in an unblinded fashion using any LDL-C lowering therapies to achieve the following LDL-C goals assigned to their group for 3 years. In group A, target values for LDL-C would be 100~<120 mg/dL for high-risk category, 120~<140 mg/dL for medium-risk category and 140~<160 mg/dL for low-risk category, according to the primary prevention criteria based on JAS Guidelines.[7] The three risk categories (low, medium and high) will be determined by the following risk stratification.

Risk stratification
Any complications of diabetes mellitus, chronic kidney diseases, non-cardiogenic cerebral infarction and peripheral arterial diseases will be classified as high risk. In the
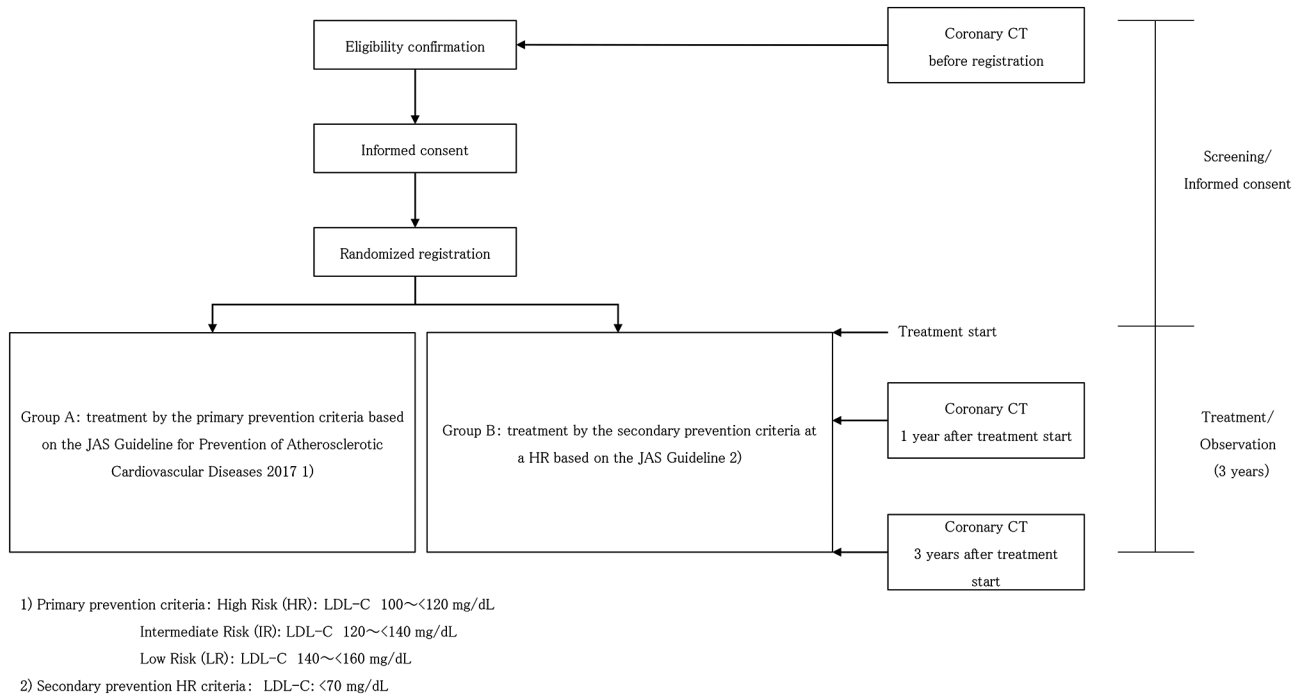
1) Primary prevention criteria: High Risk (HR): LDL-C 100～<120 mg/dL
                     Intermediate Risk (IR): LDL-C 120～<140 mg/dL
                     Low Risk (LR): LDL-C 140～<160 mg/dL
2) Secondary prevention HR criteria: LDL-C: <70 mg/dL

Figure 1 Overall schedule of this study (screening and randomisation to group A and group B, intervention and observation).

absence of these complications, risk stratification would be conducted based on the predictive model of CAD according to the Suita score,[13] which can be calculated from the following factors: sex, age, smoking/non-smoking status, blood pressure, LDL-C levels, high-density lipoprotein cholesterol levels, impaired glucose tolerance and the presence or absence of a family history of premature CAD. The probability of the onset of CAD will be calculated from the Suita score and categorized as a low risk if less than 2% for 10 years, a medium risk if 2% to 9%, and a high risk if 9% or more.

In group B, target value for LDL-C is <70 mg/dL according to the secondary prevention criteria for high risk based on the JAS Guidelines.[7]

In the LDL-C-lowering treatment, patients will be guided to diet and exercise therapies to improve lifestyle at first and then, can be additionally treated with the following therapeutic agents, if achieving the assigned target value is considered difficult after 3 months. The LDL-C levels should achieve the target value within 6 months after the start of treatment.

1. Hydroxymethylglutaryl-CoA reductase inhibitor (statin): an inhibitor of cholesterol synthesis in the liver.
2. Small intestinal cholesterol transporter inhibitor (ezetimibe): an inhibitor of cholesterol absorption in the small intestine.
3. Anion exchange resin: a promoter of bile acid excretion.

Sample size

According to the prospective observational study in patients who underwent CACT,[3] of 70 patients with vulnerable plaques, seven developed ACS and two developed stable angina, while stenotic progression was observed in 15 patients at the second CT. ACS is composed of acute myocardial infarction and unstable angina applicable to the subject of coronary artery revascularisation in major cardiovascular events included in the primary endpoint of this study or non-fatal myocardial infarction. The events corresponding to the composite outcome of the primary endpoint items of this study occurred in 24 patients (major cardiovascular events: nine patients, stenosis progression: 15 patients), until the second CT was performed to detect stenotic progression (median interval: 366 days, IQR: 203–742 days) and the incidence rate at 3 years was calculated as 34.3% (24/70). According to the meta-analysis of randomised controlled trials using statins,[14] the comparison of more versus less statin showed that major cardiovascular events were reduced by ~28% when LDL-C was lowered by 1 mmol/L (38.7 mg/dL).

Since the subjects are suspected of CAD and have undergone CACT, majority of them are expected to be high-risk patients. Therefore, if the LDL-C values would be managed according to the target values of this study, the estimates in groups A and B would be 100 to 120 mg/dL and 60 to 70 mg/dL, respectively. When trying to lower LDL-C with strict treatment such as in group B, it is expected that the LDL-C target value will not be achieved. In anticipation of this, the difference between LDL-Cs in groups A and B is considered to be about 1 mmol/L (about 38.7 mg/dL). Assuming that the occurrence of the event decreases by about 28%, similar to the results of previous studies,[14] the incidence of events in 3 years is calculated to be about 34.3% and 24.7% in groups A and B, respectively. At a significance level of α=0.025 (one-sided) and detection power of 0.8, with 353 patients per group, we will be able to reject the null hypothesis:

incidence of event in group A is less than group B. Estimating dropouts during the follow-up period to be about 5%, sample size was set as 370 in each group (740 patients in total).

Eligibility criteria
Inclusion criteria
1. Patients with a mild-to-moderate stenotic lesion in trunk, branches or periphery with a diameter of 2 mm or more, which has positive remodelling (remodelling index (RI) ≥1.1[3–5]), or with an advanced coronary artery calcification CACS >400) detected on CACT.
2. Patients aged 20 years or more at the time of consent.
3. Patients willing to provide written informed consent.

Exclusion criteria
1. Patients with a significant stenosis of the coronary artery, indicating revascularisation.
2. Patients having a history of myocardial infarction.
3. Patients having a history of coronary artery revascularisation (percutaneous coronary intervention and coronary artery bypass graft).
4. Patients whose LDL-C value already fulfils the secondary prevention criteria in JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017 at the time of registration.
5. Patients diagnosed to have familial hypercholesterolaemia (homozygote).
6. Patients with poorly controlled diabetes, with HbA1c of over 10%.
7. Subjects whose body mass index is less than 17kg/m^2.
8. Patients with chronic kidney disease, with estimated glomerular filtration rate of $30 \text{mL/min/1.73 m}^2$ or less.
9. Patients having a history of complications suspected to be related with the contrast medium.
10. Patients with thyroid disease requiring medical treatment.
11. Patients with bronchial asthma, multiple myeloma, macroglobulinaemia, tetany or pheochromocytoma.
12. Patients having a history of side effects caused by statins.
13. Patients in poor compliance with medications due to dementia.
14. Subjects judged to be inappropriate for participation in this study by the principal investigator (PI) and sub-investigators.

Blinding and randomisation
This will be an open-label, randomised controlled clinical trial. Participants and care-providers will be unblinded to the allocated group, because they cannot achieve the assigned LDL-C target during the trial without its knowledge. However, in judgement of coronary artery stenosis, the Event Evaluation Committee will perform central review with the allocation group blinded, and the central review result would be adopted in the final analysis.

Allocation of the study subjects to each group is conducted by the electronic data capture system using the minimisation method accounting for the following allocation adjustment factors: age (younger than 74 years, or 75 years or older), sex (male or female), LDL-C value before treatment (less than 140, or 140 or more), with or without any other comorbidities [diabetes, chronic kidney disease, non-cardiogenic cerebral infarction and peripheral arterial disease].

Outcomes
Primary outcomes
Composite endpoint: major cardiovascular events (death from CAD, non-fatal myocardial infarction, operation for coronary revascularisation, stroke) and stenotic progression or new stenosis development.

Secondary outcomes
1. All deaths (deaths from heart disease, non-cardiac disease, unexplained cause).
2. ACS onset (non-fatal myocardial infarction, unstable angina).
3. Operation for coronary artery revascularisation.
4. Stenotic progression or new stenosis development.
5. Exacerbation of calcification.
6. Stroke (atherothrombotic cerebral infarction, cardiogenic cerebral embolism, cerebral haemorrhage).
7. Adverse events.
8. Proportion of achievement of target value for LDL-C management.

Assessments
CT measurements
CACT images can be obtained using 64 or more slice CT according to the protocol optimised in each hospital enrolled in this study. The findings on CACT will be evaluated by two cardiologists of Central Evaluation Committee blinded to the patient's information.

Definition of coronary artery stenosis
On CACT conducted at baseline, year 1, and year 3, coronary artery stenosis is estimated and graded as none (no luminal stenosis), mild (1% to 39%), moderate (40% to 69%), severe (70% to 99%) stenosis or occluded, according to the guidelines of Society of Cardiovascular CT.[15] Stenotic progression is defined when the degree of stenosis increases by grade 1 or more. New stenosis development is defined when new stenosis higher than mild degree appears. When the stenosis is unevaluable on CACT, the lesion should be re-evaluated by CAG on catheter examination and the stenosis degree on the CAG is adopted for the analysis.

Remodelling index
Manual inspection, in both cross section and longitudinal reconstruction, is used for defining the coronary artery RI (RI=lesion diameter/reference diameter).[3–5]

Coronary artery calcification score

Calcified lesions with a peak attenuation of more than 130 Hounsfield units are quantified in whole coronary artery wall, and are then scored as CACS using Agatston method.[16]

Assessments of major cardiovascular events

The diagnosis of myocardial infarction is based on combination of symptoms and ECG findings and elevation of circulating cardiac biomarkers.[17] The patients with symptoms based on Braunwald classification, but without electrographic changes or elevation in circulating cardiac biomarkers are diagnosed with unstable angina.[18] Coronary revascularisation would be performed only in patients proven to have coronary stenosis causing ischaemia with any other modalities. Judgement of the events will be conducted by the Central Evaluation Committee.

Serious adverse events report

We will collect data on all serious adverse events (SAE) from the start to the end of the study treatment or to the 30th day from the discontinuation of study treatment. Following the initial SAE report, the PI or sub-investigators will track these cases until the events are confirmed (death, recovery, lost to follow-up).

Statistical analysis

In all efficacy evaluations, we establish the Full Analysis Set (FAS) as the main analysis set and Per Protocol Set (PPS) conforming to the study plan as reference. FAS are defined as the data of registered patients who have no serious protocol violations. PPS is defined as the population excluding patients in which there was a violation of eligibility/exclusion criteria or those who refused concomitant medicine or therapy from the FAS. Among all registered patients, a group excluding patients in which no study treatment is performed at all is called the safety analysis population (SAF).

Efficacy analysis

The superiority test (significance level α=0.025 (one-sided)) in the primary endpoint will be carried out using logistic regression analysis with covariates as allocation adjustment factors. For the secondary endpoints, we will examine the relationship with lipid management criteria using the Cox proportional hazard model for all deaths, ACS onset and operation for coronary artery revascularisation, and will explore risk factors related to development of coronary artery plaque and exacerbation of calcification using multivariate analysis with various related factors as explanatory variables.

Safety analysis

All safety analyses will be carried out for SAF. Frequency of adverse events will be calculated in each group.

Interim analysis

Existing work on 'progression of the degree of stenosis or emergence of new lesion by CACT' included in the primary endpoint is reported in only one study by Motoyama *et al*[5] and information on the incidence of events is not enough. Therefore, an interim analysis will be performed at the time when the results of follow-up evaluation by CACT at 1 year in 200 registered patients (by judgement at the implementation facility) will be collected and the sample size will be re-estimated. Specifically, using the method of Mehta and Pocock,[19] if the conditional detection power is between 50% to 80% at the time when interim analysis data are obtained, the sample size will be re-estimated. The upper limit of the sample size is 1500.

Data management

In this study, we will collect data using electronic data capture (EDC). The PI or a person nominated by the PI shall promptly input collected case information to the EDC. The transmitted electronic data would be regarded as a case report. PI will confirm that all data inputs are accurate. The data managers of respective data centres will occasionally monitor for suspicious inputs by the EDC using the central monitoring method.

Independent data monitoring committee

We will establish an independent data monitoring committee consisting of three experts in cardiology internal medicine and one expert in biostatistics. In response to consultation from the research representative, the committee will assess the efficacy and safety and make recommendations. Moreover, based on the results of interim analysis, we will decide whether to continue the study and validate the study plan modification.

Patient and public involvement

Patients and public were not involved in designing this study.

DISCUSSION

In six clinical studies, statins were administered in patients under secondary prevention and the incidence rate of coronary events in the control group (those under treatment without statin administration or standard treatment) was 5.2%–9.0% per year.[14] Accordingly, coronary artery events within 3 years are presumed to be 15.6% or more. Meanwhile, according to the observational study conducted by Motoyama *et al*, 3158 patients who underwent CACT were followed up for an average 3.9 years. As a result, 40 patients (1.4%) among a total of 2864 without high-risk plaques developed ACS, whereas 48 patients (16.3%) among a total of 294 with high-risk plaques developed ACS.[5] In similar studies conducted by several other groups, it was reported that patients with high-risk plaque detected in CACT have higher incidence rates of coronary events. This means that patients with high-risk plaques detected in CACT are considered to be at risk for coronary artery events similar to patients requiring the secondary prevention.

In patients with enlarged plaques and stenotic progression confirmed in CACT after 1 year, ACS developed in about 26.7% cases in the median follow-up period of 4 years.[5] This applies to a HR of 33.43 (95% CI of 4.13 to 78.03, p<0.0001) in multivariate analysis,[5] and enlarged plaques/stenosis development have proven to be strong predictors closely related to the onset of coronary events. Therefore, we included stenosis progression or new stenosis development as a constituent endpoint in our primary outcome.

In the mild calcification group with CACS of 0 to 99 quantified using CACT, death due to the onset of CAD or the onset of myocardial infarction was 0.4% per year, whereas in the group with high calcification represented by CACS 400 or more, the event risk was significantly high (2.4% per year).[6] In addition, when coronary artery calcification increases to CACS more than 100 per year, CAD have been shown to occur at a high rate of 10% to 15% in 3 years.[16] Thus, patients with an unstable plaque or a severe calcification detected in CACT are at high risk of coronary artery events, even if CAD has not yet developed. However, currently there is no evidence based on prospective randomised interventional studies to prove that these high-risk patients should be strictly managed to achieve lower LDL-C goals with a secondary prevention strategy even without no proven CAD.

Treatment criteria in this study are based on recommendations of the Guidelines for Prevention of Atherosclerotic Diseases established based on evidence showing the efficacy and safety in many clinical trials. All drugs and doses to be used in this study are approved and covered by national health insurance in Japan, and it is expected that adverse events in this study will not exceed those occurring in daily clinical practice.

There are several limitations in the current study. This study will be conducted in Japan and most enrolled participants will be Japanese hence, the conclusions cannot be generalised to people of other races, lifestyles or economic statuses. As this study is an open-label trial, confounding factors dependent on the allocated group, other than strict lipid management, may affect the outcomes.

In the SCOT-HEART trial, the use of CACT in addition to standard care in patients with stable chest pain resulted in a significant reduction in major cardiovascular events compared with standard care alone, suggesting that it may be attributed to more prevention therapies initiated in patients undergoing CACT.[20] However, it is unclear whether strict lipid management improved the outcomes. Our current study will contribute to the development of a better preventive therapy, by clarifying appropriate lipid management criteria for patients who have high-risk coronary atherosclerosis detected on CACT.

Ethics and dissemination

Prior to this study, the PI or sub-investigators obtained written informed consent from the patients or patients' legally acceptable representatives.

Subject information will be collected using the EDC system. In order to protect personal information, the name, address and telephone number, of the subjects will not be obtained. The medical information will be identified using the case registration number issued.

The results of this study are scheduled to be published within 2 years after study completion, via conference presentation or journal publication.

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