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Measurement of carotid artery intima-media thickness in dyslipidemic patients increases the power of traditional risk factors to predict cardiovascular events

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Abstract

A longitudinal observational study investigated whether the measurement, in clinical practice, of carotid maximum intima-media thickness (Max-IMT) could be combined with the Framingham risk score (FRS) to improve the predictability of cardiovascular events in dyslipidemic patients who are at low or intermediate risk.

Max-IMT was measured by ultrasound in 1969 patients attending a lipid clinic. The "best threshold values" (BTVs) above which we considered the Max-IMT to be abnormally high were calculated for our dyslipdemic population for each 10-year age interval in men and women. Two hundred and forty-two patients (age 54 ± 10 years; 43.8% women) with an FRS <20%, i.e. at low or intermediate risk, were monitored for more than 5 years. Twenty-four of these patients suffered a cardiovascular event within 5.1 ± 2.3 years. Both FRS and Max-IMT proved to be independent outcome predictors ($p < 0.04$, both), with a hazard ratio (HR) of 6.7 (95% CI 1.43, 31.04; $p = 0.015$) in patients in whom FRS was 10–20% and Max-IMT was above the BTV (60th percentile of Max-IMT distribution for men or 80th for women). In Kaplan–Meier analysis, the Max-IMT significantly improved the predictive value of the FRS ($\chi^2 = 8.13$, $p = 0.04$). Patients with FRS 10–20% (currently considered intermediate-risk) and also elevated Max-IMT values came into the same high-risk category as patients with FRS 20–30%.

The combination of FRS with Max-IMT measurement can be used in routine clinical practice to greatly enhance the predictability of cardiovascular events in the large number of patients who fall into the intermediate-risk category, which currently does not call for aggressive preventive measures.

Keywords: Carotid artery ultrasound; Intima-media thickness; Cardiovascular diseases; Imaging; Risk prediction

1. Introduction

Conventional risk factor assessment predicts only 60–65% of cardiac risk, and cardiac events occur in many individuals who have no established risk factors for atherosclerosis [1–3]. It has been suggested [4–7] that the combination of markers of sub-clinical atherosclerosis with algorithms for risk assessment may increase the predictability of future vascular events.

Carotid artery IMT measurement is widely available but is generally used in large-scale clinical studies of treatment effects [8,9]. However, since IMT is statistically linked to several variables associated with coronary atheromatosis

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[10–13], one would expect that its measurement could equally be applied to assess individual risk. For example, the combination of carotid IMT with diabetes risk markers was recently shown [14] to improve the prediction of cardiovascular outcome in high-risk individuals. The number of intermediate-risk potential patients, e.g. those with a Framingham risk score (FRS) of 10–20%, is high – for instance, they constitute 40% of the US population [15] – and these patients do not currently qualify for aggressive treatment [16]. However, for many clinicians this is a gray decision area. Improving the predictability for such persons would have significant impact on public health. We therefore investigated whether the non-invasive measurement of carotid IMT can be successfully combined with the FRS to adjust risk levels of asymptomatic, dyslipidemic individuals at low or intermediate risk.

2. Methods

2.1. Subjects

Almost 2000 consecutive patients (1171 men and 798 women) attending the ultrasound laboratory of the University Centre for Dyslipidemia (Niguarda Hospital, Milan, Italy) between 1986 and 2002 had their carotid IMT measured by B-mode ultrasound. This is now a routine procedure for all patients attending our Lipid Clinic. The FRS was calculated using sex-specific equations [17] predicting CHD risk of the basis of age, blood pressure [18], diabetes, smoking habits, total cholesterol and HDL-cholesterol [19].

Starting from the visit at which the ultrasound measurement was made, patients were examined clinically at least once a year and cardiac events were recorded, namely unstable angina, myocardial infarction (MI), coronary death or coronary revascularization procedures. Unstable angina and MI were diagnosed according to European Society of Cardiology (ESC) guidelines [20]. Medical records and death certificates of patients who had an event were obtained and validated by a cardiologist unaware of IMT results.

Fig. 1 shows the patient selection procedure. Only patients initially free from vascular events and with FRS <20% were selected. We compared the hazard ratio of these patients with that of another group of patients who were also asymptomatic at baseline but had a FRS between 20 and 30%. Of the 242 patients with FRS <20%, 42 had a FRS <6%, 70 had FRS between 6 and 10%, and 130 had FRS between 10 and 20%. There were 44 patients with FRS 20–30%. Over-all, 228 patients had lipid or lipoprotein abnormalities, 43 were borderline dyslipidemic, and 15 had a normal lipid/lipoprotein pattern; 131 patients were hypertensive (systolic and/or diastolic blood pressure ≥140 and ≥90 mmHg, respectively, or under treatment with hypotensive drugs); 107 patients were taking lipid-lowering drugs (statins, resins, probucol or fibrates), 54 anti-hypertensive drugs (beta-blockers, calcium antagonists, ACE inhibitors or diuretics) and 25 antiplatelet drugs. There were 54 current smokers and 102 former smokers (not smoked for at least 1 year).

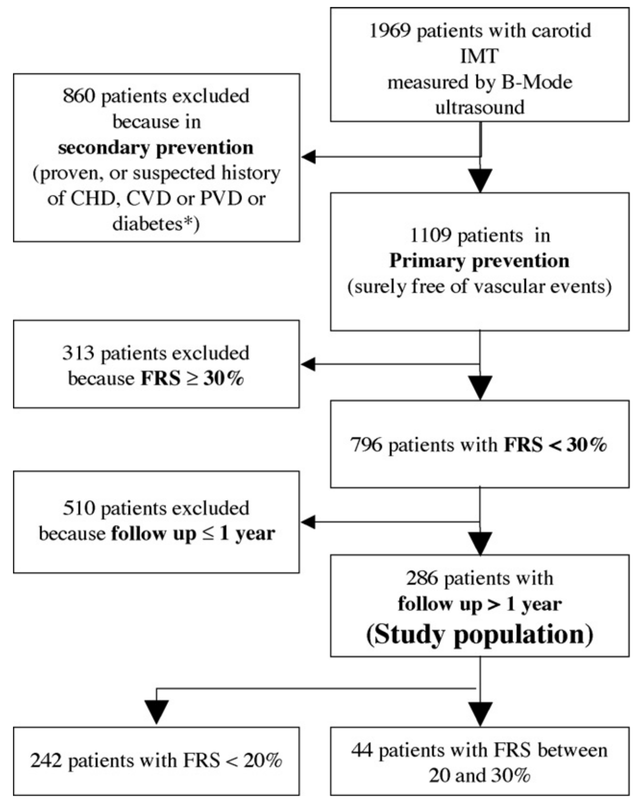

Fig. 1. Selection of the group to be studied from our total dyslipidemic population. *Diabetic patients were excluded because this condition represents a “coronary heart disease (CHD) risk equivalent” and, as such, they should be managed as patients in secondary prevention [19].

The characteristics of the 286 selected patients were similar to those of the original 1969 patients, except for a lower percentage of hypertensive patients (25.2% versus 34.1%, $p < 0.01$), a slightly lower systolic blood pressure (132 ± 15 mmHg versus 135 ± 18 mmHg, $p < 0.01$) and a higher concentration of total serum cholesterol (265 ± 57 mg/dL versus 257 ± 55 mg/dL, $p < 0.05$).

2.2. B-mode ultrasound measurements

Carotid IMT was measured in real time by using the electronic calliper of the ultrasonic device [21]. Scanning was performed by trained sonographers who were unaware of the FRS data. Near and far walls of common, internal and external carotid arteries and bifurcations were scanned in anterior, lateral and posterior projections using a standardized protocol [21]. The single highest IMT value was defined as Max-IMT. This variable incorporates the plaque(s) and represents an index of focal plaque rather than generalized wall thickening [22]. The study complies with the Declaration of Helsinki and it was approved by the Institutional Review Board. Informed consent for research purposes was obtained from all patients.

2.3. Lipids

Blood samples were collected from the antecubital vein after an overnight fast. Total cholesterol, HDL-cholesterol and triglycerides were determined in fresh serum by enzymatic methods [23,24]. Serum LDL-cholesterol was calculated by Friedewald's formula [25].

2.4. Statistical analysis

Baseline group differences were assessed by Student's *t*-test for numerical variables and by χ^2-test for categorical variables. Values of $p < 0.05$ were considered significant.

Cumulative event-free rates were estimated from Kaplan–Meier survival curves and differences were tested by the log-rank test. In some analyses, the study population was stratified into four groups according to whether IMT and FRS was above or below specified values (see Section 3). In these groups, the agreement between "the incidence of new cardiovascular events" predicted on the basis of the FRS, and the "incidence actually observed" (estimated by the Kaplan–Meyer method) was also evaluated.

A Cox Proportional Hazard Regression Model was used to control for confounding variables and to assess the independence of IMT and FRS effects.

3. Results

Among the 242 patients with FRS <20% included in the study, 24 (9.9%) developed a cardiovascular event within 5.1 ± 2.3 years: 14 had an acute MI (three fatal), 9 unstable angina and 1 had coronary revascularization. The remaining 218 had no vascular event during 5.3 ± 3.7 years. The characteristics of these low/intermediate-risk patients with and without new vascular events are shown in Table 1. Except for the lower HDL-C levels in subjects who developed a new vascular event, there were no significant differences between the two groups.

Table 1
Characteristics of patients with FRS <20%

	Without event	With event
No.	218	24
Age (year)	54.3 ± 10.5	52.9 ± 10.4
Male (%)	56.9	62.5
Framingham risk score	10.3 ± 4.8	11.8 ± 4.2
BMI (kg/m^2)	24.1 ± 2.8	24.3 ± 2.5
Never smokers (%)	51.4	45.8
Former smokers (%)	34.4	41.7
Current smokers (%)	14.2	12.5
Hypertension (%)	23.3	29.2
Systolic blood pressure (mmHg)	129.8 ± 14.8	129.4 ± 12.0
Diastolic blood pressure (mmHg)	80.7 ± 9.2	81.7 ± 10.9
Total-cholesterol (mg/dL)	262.8 ± 54.2	284.7 ± 90.6
LDL-cholesterol (mg/dL)	182.7 ± 55.2	200.3 ± 97.9
HDL-cholesterol (mg/dL)	52.1 ± 13.2	46.3 ± 9.22*
Triglycerides (mg/dL)	132.0 (34–513)	137.0 (64–474)
Max-IMT (mm)	1.56 ± 0.84	1.57 ± 0.70

Significance has been calculated after data adjustment for age. * $p < 0.05$. LDL, low-density lipoprotein; HDL, high-density lipoprotein. To convert values to millimoles per liter, multiply by 0.0259016; triglycerides. To convert values to millimoles per liter, multiply by 0.0113815.

Among the 44 patients with a FRS between 20 and 30%, 7 (16.6%) developed a new cardiovascular event within 4.5 ± 2.8 years and 35 had none after 4.1 ± 2.9 years. Compared to patients with a FRS <20%, these were older (+13.9 year, $p < 0.0001$), included more men (79.5% versus 56.2%, $p = 0.006$) and smokers (45.5% versus 14.1%, $p = 0.0001$), had lower HDL-C (-11 mg/dL, $p = 0.0001$) and greater Max-IMT (+0.61 mm, $p = 0.0001$).

In a Cox analysis performed in the FRS <20% patients, a FRS above 10%, alone, was associated with a hazard ratio of 2.31 (95% CI, 1.00, 5.4; $p = 0.05$). The inclusion into the model of carotid ultrasound information expressed as presence or absence of plaque (defined as Max-IMT value ≥ 1.3 mm) added nothing to the predictive capacity of FRS

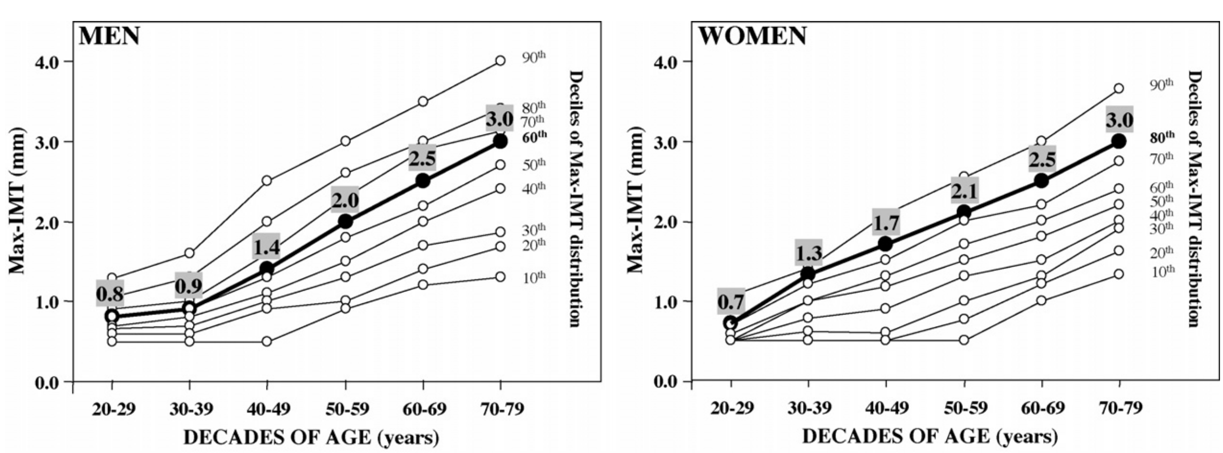

Fig. 2. Deciles of Max-IMT distribution in men (left panel) and women (right panel) calculated, in a group of 1969 Italian dyslipidemic patients, for 10-year age intervals. Highlighted values correspond to best threshold values, see Appendix A for definition, above which Max-IMT could be considered as abnormally high. These were found to be the 60th and 80th percentiles of Max-IMT distribution for men and women, respectively, for each decade of age.

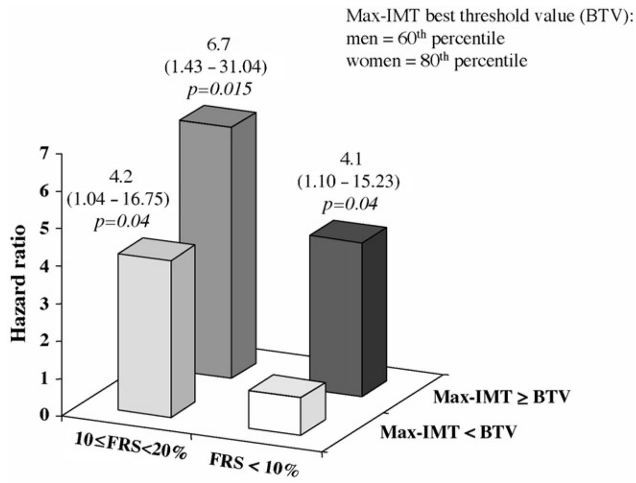

Fig. 3. Relative risk of future cardiovascular events in patients with a Framingham risk score (FRS) <20% categorized as being above or below 10% for FRS and the "BTV" values for Max-IMT. Values are hazard ratios (HRs), with 95% CIs adjusted for pharmacological treatments in parentheses.

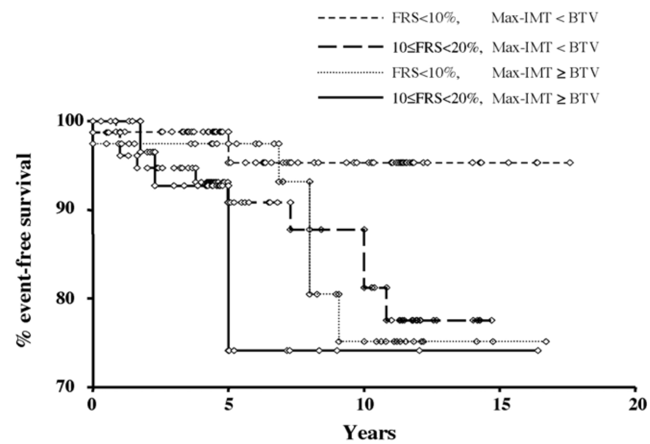

Fig. 4. Kaplan–Meier analysis of event-free survival curves for the same sub-groups as in Fig. 3. The presence of a FRS above 10% and Max-IMT above BTV (60 for men or 80 for women) was associated with the highest incidence of vascular events.

(HR = 1.30; 95% CI, 0.56, 3.03, $p = 0.55$). Similar results were obtained when plaque status was classified according to the presence or absence of an IMT ≥1.0 mm (data not shown).

Age and sex have major impact on IMT measurements. All calculations were therefore repeated after correction of the IMT for these determinants. Fig. 2 shows the deciles and the "best threshold values" (BTVs) of Max-IMT in men and women separately, calculated for 10-year age intervals. The procedure adopted to identify these BTVs is given in Appendix A. A Max-IMT value above the age-specific BTV was considered abnormally high.

Repeating the Cox analysis, using Max-IMT percentiles in place of raw Max-IMT values and BTVs as stratification tools, a FRS above 10% was associated with a HR of 2.60 (95% CI 1.07–6.3; $p = 0.03$) while a Max-IMT above BTV gave a HR of 2.42 (95% CI 1.04–5.66, $p = 0.04$), which suggests that FRS and Max-IMT are independent predictors of new cardiovascular events. No significant interaction between the two variables was observed ($\chi^2 = 0.93$, $p = 0.31$).

To investigate further the relative roles of FRS and Max-IMT in predicting new vascular events, we stratified the study population into four groups: FRS above or below 10% and Max-IMT above or below BTV. Fig. 3 shows the HR of new events for these four groups, calculated after data adjustment for pharmacological treatment. This figure clearly indicates that the concomitant presence of FRS ≥10% and Max-IMT above the BTV yielded a marked increase in the HR.

The Kaplan–Meier event-free curves for the same subgroups confirmed the association with the highest incidence of vascular events (Fig. 4).

Fig. 5 shows that, compared to low-risk patients (FRS <10%), the HR for having a new cardiovascular event in the intermediate risk group (10 ≤ FRS < 20%) increased progressively from patients with Max-IMT below to patients with Max-IMT above BTV. Interestingly, patients with a FRS

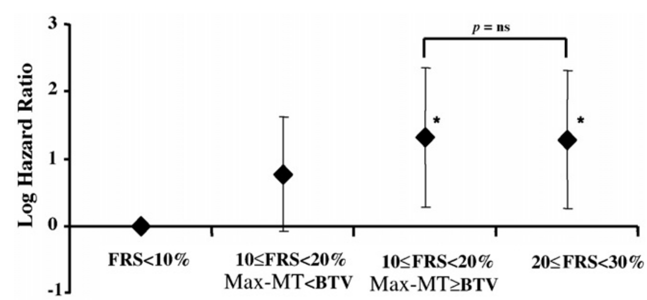

Fig. 5. Log hazard ratios in patients at low risk (FRS <10%), in patients at intermediate risk (10 ≤ FRS < 20%) above or below the BTV values for Max-IMT, and in patients at high-risk (20 ≤ FRS < 30%). *$p < 0.05$ vs. patients with FRS < 10.

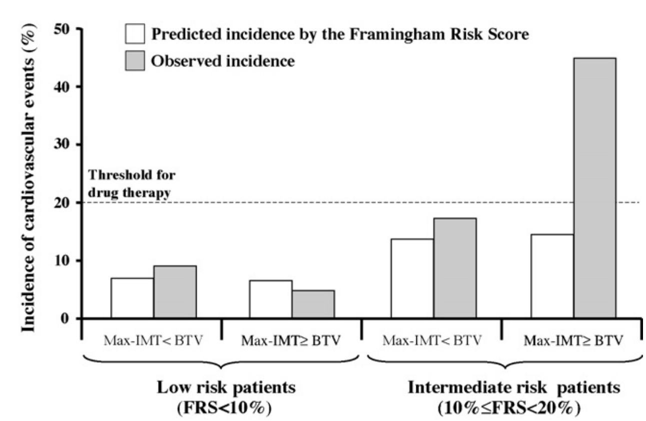

Fig. 6. Comparison between the incidence of new cardiovascular events predicted on the basis of FRS and the incidence actually observed (estimated by the Kaplan–Meyer method) in patients at low or intermediate risk stratified according to the presence of an Max-IMT above or below the appropriate BTV.

between 20 and 30% had no higher risk ($\chi^2 = 0.19$, $p = 0.67$), even after data adjustment for drug treatments.

Fig. 6 shows the incidence of new cardiovascular events predicted on the basis of the FRS versus the observed incidence in patients with Max-IMT either above or below the BTV. The figure shows that, for patients with FRS between 10 and 20%, a Max-IMT above the BTV had over three times greater predictive power than FRS alone.

4. Discussion

This study shows that for patients with FRS below 10%, measurement of carotid IMT does not increase the hazard ratio, but that if the FRS is between 10 and 20% the combination with a measure of IMT above the best threshold value (as defined in Appendix A) increases the hazard ratio more than three-fold, to equal the HR for patients with FRS between 20 and 30%.

Several studies have established that markers of subclinical disease can improve the prediction of individual risk of new cardiovascular events by traditional risk factors [4,6,7,12,26,27], e.g. the combination of IMT measurement with FRS in diabetics [14]. Most studies have used a single threshold point above which a carotid artery IMT should be considered abnormal, e.g. an IMT $\geq$1 mm, independent of age or gender [6,7,26,28]. However, in populations affected by major risk factors (e.g. hypertension or dyslipidemia), almost everyone older than 50 has an IMT $\geq$1 mm (see also Fig. 2). In our study, addition to the FRS of the “plaque status”, without reference to sex and age, did not significantly improve the predictive power of the FRS; indeed, the Wald Chi-square increased by just 0.32 (from 5.97, FRS only, $p = 0.56$).

Some authors have tried to overcome these limitations by stratifying IMTs into percentiles [29–31]. Here too, the upper limit of normal IMT was chosen arbitrarily, frequently being set at the 75th percentile of the IMT distribution of a general healthy population, whereas the IMT of almost all subjects affected by vascular risk factors is above the 75th percentile of a general healthy population.

The present study has identified the threshold values for Max-IMT that allow the best prediction of new cardiovascular events in a dyslipidemic population, and it provides a new tool for the assessment of dyslipidemic patients at intermediate risk as judged by the FRS. A Max-IMT value above the appropriate BTV (as defined in Appendix A) in such an individual would lead to their reclassification as high-risk (equivalent to FRS $\geq$20), with consequent effects on therapy or preventive action. These results are independent of a plaque/no-plaque definition; in fact, with the present approach, risk stratification is possible equally well in the earliest decades, where the probability of finding plaques is low, as at older ages, where on the contrary the presence of plaques may be a normal feature even in the absence of important vascular risk factors.

After completing the larger part of the study, we started to use this procedure routinely in our institution, i.e. to evaluate Max-IMT in all patients in whom the clinical status was uncertain. Surprisingly, we have found (cf. also [32]) several individuals with elevated HDL-cholesterol levels who have Max-IMT values well above the limit for their age group and with a high incidence of coronary events (data not shown).

We should point out some limitations to the recommended procedure. First, it cannot be applied to the general population or to patients with vascular risk factors other than dyslipidemia, because our BTVs of Max-IMT were derived from subjects attending a lipid clinic. Second, the reported BTVs were derived from an Italian population and, as with coronary calcium [33], IMTs may differ for patients in different countries and continents even when the same vascular risk factors are present. Thus, although the general approach here suggested should be valid for any kind of population, local age- and sex-specific BTVs must be calculated for populations different from the one studied here.

5. Conclusions

We have shown that, even when determined in routine clinical practice, carotid artery Max-IMT measurement can enhance the standard cardiovascular risk prediction in dyslipidemic patients at intermediate risk. The finding that FRS and Max-IMT make independent contributions to prediction suggests that individual susceptibility to carotid atherosclerosis may be affected by genetic, environmental, socioeconomic, infectious or lifestyle-related factors that are not considered in the FRS.

Acknowledgment

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Appendix A

Best threshold values were calculated as follows. Deciles of Max-IMT of the total population of 1969 were analyzed separately for men and women in 10-year age intervals (Fig. 2). The Max-IMT percentile for each patient was derived from his/her age and sex distribution—for instance, a 53-year-old man with a Max-IMT of 2.99 mm had a Max-IMT percentile of 90, since 2.99 lies in the 90th percentile of the relevant Max-IMT distribution. The percentiles for the 286 patients included in the study were then examined to find the threshold value above which a Max-IMT could be considered high, and which then gave the best predictive outcome as to new cardiovascular events. These are shown on the thick lines in Fig. 2 and proved to be the 60th percentile for men and the 80th percentile for women in the corresponding age-specific distributions.

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