Long-Term (>10 Years) Prognostic Value of *Dobutamine* Stress Echocardiography in a High-Risk Cohort

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The prognostic value of dobutamine stress echocardiography (DSE) at >10-year follow-up is unknown. The aim of this study was to assess the very long-term prognostic value of DSE in a high-risk cohort of patients with known or suspected coronary artery disease. This prospective, single-center study included 3,381 patients who underwent DSE from January 1990 to January 2003. Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and during recovery. Follow-up events were collected and included overall mortality, cardiac death, nonfatal myocardial infarction, and revascularization. The incremental value of DSE in the prediction of selected end points was evaluated using multivariate Cox proportional hazard analysis. During a mean follow-up of 13 ± 3.2 years (range 7.3 to 20.5 years), there were 1,725 deaths (51%), of which 1,128 (33%) were attributed to cardiac causes. Patients with an abnormal DSE had a higher mortality rate (44% vs 35% at 15-year follow-up, p <0.001) than those with a normal DSE. When comparing echocardiographic variables at rest to variables at maximum dose dobutamine, the chi-square of the test improved from 842 to 870 (p <0.0001) and from 684 to 740 (p <0.0001) for all-cause mortality and cardiac death, respectively. DSE provided incremental value in predicting all-cause mortality, cardiac death, and hard cardiac events. There seems, however, to be a "warranty period" of approximately 7 years, when the survival curves of a normal and abnormal DSE no longer diverge. **(Am J Cardiol 2016;117:1078−1083)**

Exercise electrocardiography is the most frequently used method for noninvasive evaluation of coronary artery disease (CAD). Still, a substantial number of patients have an impaired exercise capacity, because of a weak general physical condition, neuropathy, or peripheral vascular disease. Dobutamine stress echocardiography (DSE) has been reported as a safe[1] and effective noninvasive tool to provide diagnostic and prognostic information in various clinical scenarios.[2−7] Currently, it is not known whether the prognostic value of DSE in patients with limited exercise capacity is preserved at very long-term (>10 years) follow-up. The goals of this study were to assess the very long-term outcome after DSE in a high-risk group of consecutive patients and to evaluate whether DSE has incremental prognostic value over clinical variables and echocardiographic data at rest.

Methods

This prospective study included 3,875 consecutive patients at high risk with known or suspected CAD, who were unable to perform an adequate exercise test. Indications for DSE were diagnosis of CAD (54%), preoperative evaluation before noncardiac surgery (34%), and risk stratification after myocardial infarction (MI, 12%). Of all patients who underwent DSE, 30% had a history of typical angina, and 13% had a history of atypical angina.[8] Data were collected from patients who underwent DSE from January 1990 to January 2003 at the Thoraxcenter, Rotterdam, the Netherlands. Follow-up data at shorter intervals and of specific subgroups of this study cohort have been previously published.[2,5,9] Thirty-nine patients were lost to follow-up, and 455 patients underwent early coronary revascularization in the first 60 days after DSE and were excluded from the analysis because referral for revascularization within this period is likely to be based on DSE results. The final population of this study consisted of 3,381 patients. This study was not subject to the Dutch Medical Research Involving Human Subjects Act. Therefore, approval from the local research ethics committee to conduct this prospective follow-up study was not required at the time of enrollment. The study was conducted according to the Declaration of Helsinki.[10] All patients consented participation in this study.

Clinical characteristics including hypertension, hypercholesterolemia, smoking, previous MI, a history of heart failure, and/or revascularization were recorded at the time of DSE in a computerized database. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol >200 mg/dl or the use of cholesterol-lowering agents. Heart failure was defined according to the New York Heart Association classification and based on established guidelines at the time of diagnosis.[11]

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See page 1082 for disclosure information.

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After baseline echocardiography, dobutamine was infused at a starting dose of 5 μg/kg/min for 3 minutes followed by 10 μg/kg/min for 3 minutes (low-dose stage). The dobutamine dose was increased by 10 μg/kg/min every 3 minutes up to a maximum dose of 40 μg/kg/min. Atropine (up to 1 mg) was administered intravenously at the end of the last stage if the target heart rate was not achieved. End points of the test were an achievement of the target heart rate (85% of the maximal heart rate predicted for age), the maximal dose of dobutamine and atropine, >2 mV downsloping ST-segment depression measured 80 ms from the J point compared with baseline, hypertension (blood pressure >240/120 mm Hg), a decrease in systolic blood pressure of >40 mm Hg, and significant arrhythmias.

Two-dimensional echocardiographic images were acquired at rest, during dobutamine stress, and during recovery using standard views. Regional wall motion and systolic wall thickening were scored on a 5-point scale using a standard 16-segment left ventricular model. Ischemia was defined as new or worsened wall motion abnormalities (WMA) during stress indicated by an increase of wall motion score ≥1 grade in ≥1 segment. A biphasic response in an akinetic or severely hypokinetic segment was considered as an ischemic response. Ischemia was not considered present when akinetic segments at rest became dyskinetic during stress.[12] For each patient, a wall motion score index (WMSI) was calculated by dividing the sum of segment scores by the total number of interpreted segments. The test was considered abnormal if WMA were seen either at rest or during stress.

Outcome data were obtained by a questionnaire, evaluation of hospital records, contacting the patient's general practitioner, and/or review of civil registries. The cause of death was retrieved at Statistics Netherlands (www.cbs.nl). This permitted high accuracy for determination of survival status. Deaths were classified as either documented cardiac death or other. Before contacting the patient, the online municipal civil registry was used to determine the patient's present survival status. Survival status was retrieved in 99% of the patients. Questionnaires were sent to all patients alive. The response rate of this questionnaire was 83%. The date of response was used to calculate follow-up time. Follow-up events noted were overall mortality, hard cardiac events (non-fatal MI and cardiac death), and revascularization.

Continuous data are expressed as mean values ± SD. The Student *t* test was used to analyze continuous data, and the chi-square test was used for differences between proportions. The incremental value of DSE over the clinical variables in the prediction of selected end points was evaluated using multivariate Cox proportional hazard analysis (SPSS Software, version 21.0) including a model with baseline characteristics and clinical variables. Only variables that were significant in a univariate model were added to the multivariate model. Using a stepwise model, echocardiographic variables at rest were then added to the clinical model to investigate the increase in chi-square value of the model. Finally, the variables at peak-dose dobutamine were added to the model. The test was considered of additional value if there was a significant increase in chi-square value at the third step of the test. The echocardiographic variables that were added at rest and peak-dobutamine dose were heart rate, systolic and diastolic blood pressure, rate pressure product (defined as maximum heart rate times the maximum systolic blood pressure), WMSI, and WMA. The probability of survival was calculated using the Kaplan−Meier method, and survival curves were compared using the log-rank test. To determine the warranty period of DSE, the Cox proportional hazard analysis for an abnormal DSE was repeated at 1, 2, 3, and so on years of follow-up. A p value <0.05 was considered statistically significant.

Table 1
Clinical characteristics

Variable	n = 3,381
Men	2,275 (67%)
Age (yrs)	61.4 ± 12
Hypertension	1,005 (30%)
Hypercholesterolemia	770 (23%)
Smoking	988 (29%)
Diabetes mellitus	378 (11%)
Heart failure	454 (13%)
Coronary artery disease	1,525 (45%)
Beta-blockers	1,116 (33%)
Calcium-channel blockers	816 (24%)
Angiotensin-converting-enzyme inhibitor	845 (25%)
Diuretics	477 (14%)
Nitrates	1,031 (31%)

Results

Mean age at time of DSE was 61 ± 12 years. There were 2,275 men (67%) and 1,106 women (33%). Forty-five percent of the patients had known CAD. Clinical characteristics are presented in Table 1. The test was terminated for achievement of the target heart rate in 89% of the patients, maximal dobutamine/atropine dose in 3%, ST-segment changes in 3%, arrhythmias in 1%, severe angina in 1%, abnormal blood pressure in 1%, and other symptoms in 2%. Five hundred sixty-eight (17%) patients had typical angina during dobutamine stress.

DSE was normal in 1,170 of the patients (35%). Ischemia on DSE was detected in 1,610 patients (48%); of which 1,441 (90%) had WMA at rest. Six hundred one (18%) patients had WMA at rest alone. During a mean follow-up of 13 ± 3.2 years (range 7.3 to 20.5 years), there were 1,725 deaths (51%), of which 1,128 (33% of total study cohort) were attributed to cardiac causes. Two hundred ninety-seven patients (8.8%) had a nonfatal MI, and 793 patients were revascularized (23.5%) at during follow-up. The annualized mortality rate of patients who underwent revascularization after an ischemic event was comparable to the group who did not undergo percutaneous coronary intervention (3.9% vs 4.2%, respectively).

Cumulative survival curves (Figure 1) showed a significantly better survival of patients with normal DSE in comparison with abnormal DSE (76% vs 69% at 5 years, 57% vs 50% at 10 years, and 44% vs 35% at 15 years; overall p <0.001). Figure 1 illustrates that also for the end points cardiac death (87% vs 77% at 5 years, 74% vs 62% at 10 years, and 63% vs 47% at 15 years; overall p <0.001) and hard cardiac events (82% vs 69% at 5 years, 65% vs

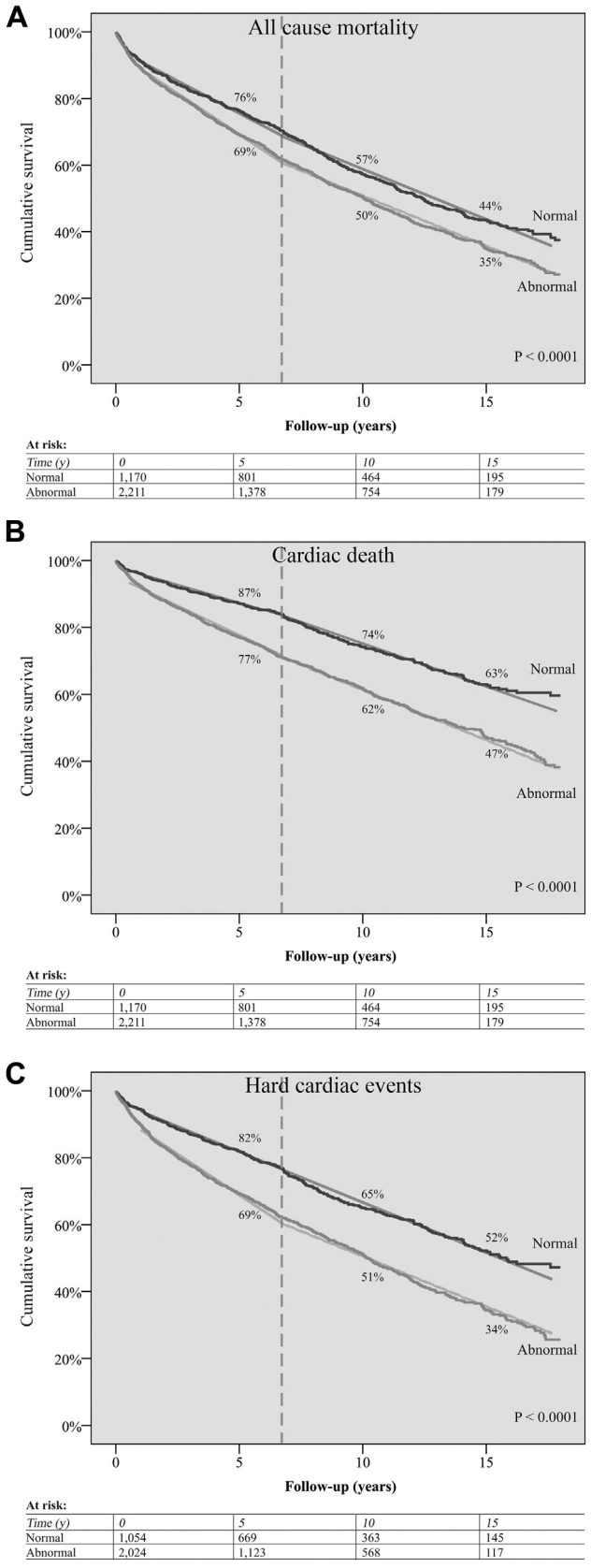

Figure 1. Kaplan−Meier survival curves for all-cause mortality *(A)*, cardiac death *(B)*, and hard cardiac events *(C)* in patients with normal *(dark gray)* versus abnormal *(light gray)* DSE. The *dummy lines* illustrate that the curves start to run parallel at approximately 7 years *(dashed line)*.

51% at 10 years, and 52% vs 34% at 15 years; overall p <0.001), the population with a normal DSE had significant lower chance of adverse events.

Univariate and multivariate predictors associated with an increased risk of all end points of interest are presented in Tables 2 and 3. Echocardiographic variables at peak-dose dobutamine significantly increased the value of the test for all end points. When comparing echocardiographic variables at rest to variables at maximum dose dobutamine, the chi-square of the test improved from 842 to 870 (p <0.0001) and from 684 to 740 (p <0.0001) for all-cause mortality and cardiac death, respectively. WMSI during stress predicted both all-cause mortality and cardiac death. At 5 years of follow-up, the hazard ratio of having an abnormal DSE reached a maximum of 1.37 and started to decrease after 7 years of follow-up.

Discussion

DSE is a commonly used tool to predict short to medium-term outcome of patients with limited exercise capacity. In this high-risk patient cohort, DSE has incremental value at very long-term follow-up for predicting all end points of interest in a consecutive population with known or suspected CAD. DSE added prognostic value to clinical variables and stress test data in predicting all-cause mortality, cardiac death, and hard cardiac events. Heart rate, WMSI, and new or worsened WMA during peak-dose dobutamine were significant predictors depending on the end points of interest (Tables 2 and 3). Kaplan−Meier curves confirmed the previously described findings because outcome for all end points of interest was in favor of a normal DSE in comparison with an abnormal DSE at 18 years after initial testing (p <0.001).

Although the Kaplan−Meier curves showed a significant improved outcome in favor of a normal DSE for all end points, it is of interest to see that the curve of all-cause mortality (Figure 1) diverges up to approximately 7 years after DSE. At this point, the test seems to stop to further discriminate between abnormal and normal DSE and both lines start to run parallel. This effect is less pronounced in the Kaplan−Meier curves of cardiac death (Figure 1) and hard cardiac events (Figure 1), but it suggests a certain "warranty period" of a DSE. This in line with what we observed in the diabetic subcohort of this population,[5] where a similar phenomenon was observed at 7 years.

The prognostic significance of DSE at short- to medium-term follow-up has been demonstrated in several studies.[13−17] Currently, there are no studies evaluating the very long-term prognostic role of DSE. In a meta-analysis, Shaw et al[18] investigated the prognostic role of dipyridamole and DSE in preoperative screening before vascular surgery. The meta-analysis included 15 studies, of which 5 studies (n = 445) were based on studies on DSE. The analysis demonstrated that echocardiographic WMA were predictive of adverse perioperative outcomes. Their analysis supports pharmacologic stress imaging as a tool for preoperative screening in patients at intermediate risk. These previous studies provide useful information about the clinical importance of DSE, but the very long-term prognostic value of a DSE remains unclear. This study provides unique

Table 2
Independent predictors of all-cause mortality

	Univariate	(1): Clinical	(2): (1) + DSE At Rest	(3): (2) + DSE At Peak
		HR (CI)	HR (CI)	HR (CI)
Male gender	1.45 (1.31-1.62)	1.39 (1.25-1.55)	1.39 (1.25-1.55)	1.38 (1.23-1.54)
Age	1.06 (1.05-1.06)	1.06 (1.05-1.06)	1.06 (1.06-1.07)	1.06 (1.06-1.07)
Coronary artery disease	Not significant	-	-	-
Heart failure	1.91 (1.68-2.17)	1.59 (1.38-1.82)	1.36 (1.18-1.58)	1.40 (1.21-1.62)
Diabetes mellitus	1.44 (1.25-1.65)	1.49 (1.30-1.72)	1.41 (1.22-1.62)	1.40 (1.21-1.61)
Hypertension	Not significant	-	-	-
Hypercholesterolemia	0.71 (0.62-0.80)	0.74 (0.65-0.84)	0.68 (0.60-0.77)	0.69 (0.60-0.78)
Smoking	1.24 (1.12-1.37	1.42 (1.28-1.57)	1.42 (1.28-1.58)	1.42 (1.28-1.58)
Beta-blockers	0.81 (0.73-0.89)	0.86 (0.77-0.96)	Not significant	-
Calcium-channel blockers	Not significant	-	-	-
Angio-converting enzyme inhibitors	1.29 (1.16-1.43)	Not significant	-	-
Diuretics	1.73 (1.53-1.97)	1.33 (1.15-1.53)	1.23 (1.07-1.42)	1.23 (1.07-1.42)
Digoxin	2.24 (1.88-2.68)	1.36 (1.12-1.65)	Not significant	-
Nitrates	Not significant	-	-	-
Heart rate rest	1.11 (1.07-1.15)	-	1.13 (1.09-1.18)	Not significant
Systolic blood pressure rest	1.05 (1.03-1.07)	-	Not significant	-
Diastolic blood pressure rest	Not significant	-	-	-
Rate pressure product rest	1.01 (1.00-1.01)	-	Not significant	-
Wall motion score index rest	1.48 (1.38-1.59)	-	1.32 (1.22-1.44)	Not significant
Rest wall motion abnormalities	1.29 (1.17-1.42)	-	Not significant	-
Heart rate peak	0.97 (0.95-0.99)	-	-	Not significant
Systolic blood pressure peak	0.97 (0.95-0.99)	-	-	Not significant
Diastolic blood pressure peak	0.95 (0.92-0.98)	-	-	Not significant
Rate pressure product peak	1.00 (1.00-1.00)	-	-	Not significant
Wall motion score index peak	1.54 (1.43-1.67)	-	-	1.35 (1.23-1.48)
Peak wall motion abnormalities	1.37 (1.25-1.51)	-	-	Not significant
Any wall motion abnormalities	1.27 (1.15-1.41)	-	-	Not significant
X2-test		842	870	870
p-value		**-**	**P < 0.0001**	**P < 0.0001**

information on the very long-term prognostic value of the test in a consecutive population of subjects with known or suspected CAD. It demonstrates the clinical importance of DSE results for assessment of very long-term outcome.

The event rate in this present study is high (51% of the patients died during follow-up). There are multiple factors that may explain the relatively high event rate in this study. First, this cohort is a high-risk group, the mean age was 61 years and 45% had known CAD, whereas 65% of the patients had an abnormal DSE. Second, all patients underwent DSE because of limited exercise capacity. The inability to perform an adequate exercise test is an indicator of adverse outcome in itself. Third, the follow-up of this cohort was nearly complete. Finally, this study has follow-up period of >10 years, which is significantly longer than previous studies.

Although this study included a high-risk population, Table 1 demonstrates that patients seemed undertreated according to current standards. Inclusion of patients in this study started as early as 1990, a time at which medical treatment was suboptimal compared with current standards, as has been demonstrated in the EUROASPIRE (EUROpean Action on Secondary and Primary prevention through Intervention to Reduce Events) registry.[19] Referral to coronary revascularization (23.5%) was also relatively low given the 48% of the patients with detected ischemia. However, previous studies have demonstrated that the timing of revascularization requires careful consideration.[20] Patients with no or mild symptoms and little ischemia can safely be treated with medical treatment alone. Furthermore, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial[21] has demonstrated that clinical outcome in patients with stable angina does not significantly differ between patients who receive an initial therapy of coronary revascularization and optimal medical therapy compared to patients with optimal medical therapy alone.

The American College of Cardiology recommends pharmacologic stress with either nuclear myocardial infusion imaging or echocardiography for risk assessment in patients with stable ischemic heart disease who are either unable to exercise to an adequate workload regardless of interpretability of electrocardiogram, patients with left bundle branch block on electrocardiogram regardless of ability to exercise to an adequate workload or patients who are being considered for revascularization of known coronary stenosis of unclear physiological significance.[22] The appropriateness criteria for stress echocardiography formulated by the American College Cardiology illustrate these recommendations and add several clinical scenarios in which stress echocardiography is the preferred technique or can be considered.[23] The present study demonstrates that

Table 3
Independent predictors of cardiac death

	Univariate	(1): Clinical	(2): (1) + DSE At Rest	(3): (2) + DSE At Peak
	HR (CI)	HR (CI)	HR (CI)	HR (CI)
Male gender	1.56 (1.36-1.78)	1.46 (1.27-1.67)	1.40 (1.22-1.61)	1.38 (1.20-1.59)
Age	1.07 (1.05-1.05)	1.06 (1.06-1.07)	1.06 (1.06-1.07)	1.06 (1.05-1.07)
Coronary artery disease	1.33 (1.18-1.50)	Not significant	-	-
Heart failure	2.47 (2.14-2.86)	2.00 (1.70-2.35)	1.60 (1.36-1.89)	1.65 (1.40-1.94)
Diabetes mellitus	1.40 (1.17-1.67)	1.42 (1.19-1.70)	1.32 (1.11-1.58)	1.30 (1.09-1.56)
Hypertension	Not significant	-	-	-
Hypercholesterolemia	0.78 (0.67-0.90)	0.80 (0.69-0.94)	0.72 (0.62-0.84)	0.73 (0.63-0.86)
Smoking	1.36 (1.20-1.54)	1.54 (1.36-1.74)	1.54 (1.35-1.74)	1.53 (1.35-1.73)
Beta-blockers	0.81 (0.71-0.92)	0.86 (0.75-0.98)	Not significant	-
Calcium-channel blockers	Not significant	-	-	-
Angio-converting enzyme inhibitors	1.48 (1.30-1.68)	Not significant	-	-
Diuretics	1.95 (1.67-2.26)	1.34 (1.12-1.59)	Not significant	-
Digoxin	2.68 (2.18-3.28)	1.46 (1.17-1.83)	1.36 (1.09-1.70)	1.33 (1.06-1.66)
Nitrates	1.32 (1.16-1.49)	Not significant	-	-
Heart rate rest	1.12 (1.06-1.17)	-	1.13 (1.08-1.18)	1.14 (1.09-1.19)
Systolic blood pressure rest	1.03 (1.01-1.06)	-	Not significant	-
Diastolic blood pressure rest	Not significant	-	-	-
Rate pressure product rest	1.01 (1.00-1.01)	-	Not significant	-
Wall motion score index rest	1.78 (1.64-1.94)	-	1.54 (1.39-1.69)	Not significant
Rest wall motion abnormalities	1.70 (1.50-1.93)	-	Not significant	-
Heart rate peak	0.96 (0.94-0.99)	-	-	Not significant
Systolic blood pressure peak	0.95 (0.93-0.97)	-	-	Not significant
Diastolic blood pressure peak	0.93 (0.89-0.96)	-	-	Not significant
Rate pressure product peak	1.00 (0.99-1.00)	-	-	Not significant
Wall motion score index peak	1.93 (1.77-2.12)	-	-	1.63 (1.47-1.81)
Peak wall motion abnormalities	1.76 (1.57-1.99)	-	-	Not significant
Any wall motion abnormalities	1.70 (1.49-1.94)	-	-	Not significant
X2-test	-	684	734	740
p-value	**-**	**-**	**P <0.0001**	**P <0.0001**

DSE is a valuable test in predicting all-cause mortality, cardiac death, and hard cardiac events, even at very long-term follow-up. The long-lasting follow-up of this study is unique and reinforces the finding from shorter follow-up studies that stress echo is a powerful prognostic test. There seems to be a "warranty period" of approximately 7 years after which a DSE start to lose its ability to further discriminate between a normal and abnormal DSE.

This study has some limitations. First, because of the clinical factors leading patients to be referred for DSE at the time of initial testing, they are likely to have had increased risk for adverse events with a worse prognosis than a general population. This may limit application of the present findings to patients suspected for CAD in general. Furthermore, left ventricular ejection fraction was not available in all patients because it was only measured on indication and could therefore not be used in the analysis.

Disclosures

The authors have no conflicts of interest to disclose.

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