Review Paper

The Obesity, Metabolic Syndrome, and Type 2 Diabetes Mellitus Pandemic: II. Therapeutic Management of Atherogenic Dyslipidemia

Henry N. Ginsberg MD;[1] Paul R. MacCallum PhD[2]

Strategies for the effective management of cardiovascular risk factors in patients with the metabolic syndrome (MS) or type 2 diabetes mellitus (T2DM) are essential to help reduce cardiovascular morbidity and mortality. Treatment strategies should be multifactorial and include the promotion of therapeutic lifestyle changes, as well as pharmacologic therapies to treat individual risk factors according to current guidelines. In an accompanying article, the importance of atherogenic dyslipidemia as a risk factor for the development of cardiovascular disease in patients with MS or T2DM was highlighted. Current treatment options for managing this characteristic form of atherogenic dyslipidemia are limited and tend to be only moderately effective. The focus of this review is the current pharmacotherapies available for the management of atherogenic dyslipidemia in patients with the MS or T2DM, highlighting the rationale for combining available treatments. Novel strategies currently in clinical development are also discussed. J Clin Hypertens (Greenwich). *2009;11:520–527.* ©*2009 Wiley Periodicals, Inc.*

From the Department of Medicine and the Irving Institute for Clinical and Translational Research, College of Physicians and Surgeons, Columbia University, New York, NY;[1] and Envision Pharma, Horsham, UK[2]
Address for correspondence:
Henry N. Ginsberg, MD, Irving Institute for Clinical and Translational Research, College of Physicians and Surgeons, PH 10-305, 630 West 168th Street, New York, NY 10032
E-mail: hng1@columbia.edu
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MANAGEMENT OF DYSLIPIDEMIA IN THE METABOLIC SYNDROME AND TYPE 2 DIABETES MELLITUS

Atherogenic dyslipidemia in patients with the metabolic syndrome (MS) or type 2 diabetes mellitus (T2DM) is characterized by low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides and apolipoprotein B (apoB), and a shift in the low-density lipoprotein (LDL) pool towards small, dense LDL particles. While not typically observed in these patients, elevated LDL cholesterol (LDL-C) is well established as a major cause of cardiovascular events in the general population.[1] Consensus-based guidelines emphasize LDL-C as the primary target for dyslipidemia management in patients with MS or T2DM.[1,2]

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and American Diabetes Association (ADA) guidelines both recommend an LDL-C target for patients with T2DM of <100 mg/dL.[1–3] In patients with MS, the NCEP ATP III guidelines state that LDL-C target is defined by the estimated absolute risk of coronary heart disease (CHD)/cardiovascular disease (CVD).[1] A recent update to the NCEP ATP III guidelines suggests a more aggressive goal of <70 mg/dL for patients at very high CVD risk.[4]

This includes individuals with preexisting CVD and either diabetes or multiple poorly controlled risk factors or MS.

Other components of atherogenic dyslipidemia are considered secondary targets. For patients with MS, NCEP ATP III guidelines identify non–HDL-C as a secondary target in persons with high triglycerides (200–499 mg/dL). Non-HDL goals are 30 mg/dL higher than LDL goals. No treatment goal is specified for raising HDL.[1] In patients with T2DM, ADA guidelines recommend target goals for triglycerides and HDL-C of <150 mg/dL and >40 mg/dL (>50 mg/dL in women), respectively.[2]

CURRENT PHARMACOLOGIC THERAPIES FOR MANAGEMENT OF DYSLIPIDEMIA IN MS AND T2DM

Guidelines for management of MS[5] and diabetes[2] recommend statins to reduce elevated LDL-C levels, followed by fibrates and niacin to lower triglyceride and elevate HDL-C levels. Statins achieve LDL-C reductions of up to 55%,[1] and also lower triglycerides (15%–40%) and modestly raise HDL-C (2%–10%). Fibrates reduce triglycerides (25%–50%) and increase HDL-C (5%–15%), with variable effects on LDL-C.[1,6,7] Niacin-based formulations provide the greatest HDL-C elevations (up to 35%),[1] while reducing triglycerides (20%–30%) and LDL-C (10%–15%).[2] Although niacin has been noted to increase blood glucose in diabetic patients, this effect is usually manageable by adjusting antidiabetic therapy.[8] However, niacin can also exacerbate insulin resistance, with increases in insulin levels observed in diabetics and nondiabetics.[9] Other LDL-C–lowering agents (including ezetimibe, bile acid sequestrants, and plant sterol and stanol esters) may be particularly efficacious for attainment of LDL-C <70 mg/dL in patients already treated with a statin, or in patients who are intolerant to statin therapy. Omega-3 fatty acids or thiazolidinediones, particularly pioglitazone, may improve triglyceride and HDL-C abnormalities.

Statins

Post-hoc subgroup analyses of statin trials have indicated reduced CVD risk in patients with MS or T2DM.[10–15] In the Scandinavian Simvastatin Survival Study (4S),[16] simvastatin significantly reduced major coronary events (relative risk [RR]=0.58 vs placebo; *P*=.001) in diabetic patients (n=483).[11] Simvastatin-associated absolute risk reductions in all-cause mortality, coronary mortality, and coronary events were greater in nondiabetic patients with MS (n=893) than in those without (n=3040), reflecting the greater absolute risk in patients with MS.[12]

In the Cholesterol and Recurrent Events (CARE) study,[17] diabetic patients (n=586) experienced a reduced RR of coronary events with pravastatin (25% vs placebo; *P*=.05). This change was similar in magnitude to that in nondiabetic patients.[13] Similarly, in the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) study,[18] pravastatin reduced the risk of a major coronary event by 19% (*P*=.11) and any cardiovascular event by 21% (*P*<.008) in diabetic patients (n=1077).[14] Recent subanalyses of the Treating to New Targets (TNT) study[19] showed that intensive therapy with atorvastatin 80 mg/d significantly reduced major cardiovascular events compared with atorvastatin 10 mg/d by 25% in 1501 patients with CHD and diabetes[20] and by 27% in 5584 patients with CHD and MS.[21]

In the Heart Protection Study (HPS),[22] simvastatin reduced cardiovascular events in approximately 6000 diabetic patients by a magnitude similar to that in the total study population.[23] In the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA), which enrolled hypertensive patients with no CHD,[24] atorvastatin reduced major cardiovascular events or procedures by 23% compared with placebo in 2532 diabetic patients (hazard ratio [HR], 0.77; *P*=.036), a similar RR to that in nondiabetic patients.[15] Similarly, in the primary prevention West of Scotland Coronary Prevention Study (WOSCOPS),[25] pravastatin reduced the risk of CHD events by a similar magnitude in men with and without MS (HR vs placebo: 0.73 and 0.69, respectively).[10]

These data were reinforced by the results of the prospective Collaborative Atorvastatin Diabetes Study (CARDS), which enrolled 2838 diabetic patients with no CVD history.[26] Compared with placebo, patients receiving atorvastatin 10 mg/d had a 37% reduction (*P*=.001) in major cardiovascular events. Atorvastatin reduced acute CHD by 36%, coronary revascularizations by 31%, and stroke by 48%. However, in the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin Dependent Diabetes Mellitus (ASPEN), rates of the composite cardiovascular event end point in 2410 diabetic patients were not significantly reduced by atorvastatin 10 mg/d compared with placebo.[27] However, it should be noted that this study population had pretreatment LDL-C levels below guideline targets, and the findings are therefore not discordant with the imperative to treat the majority of diabetic patients to below LDL-C goal levels.

Fibrates

Fibrates have demonstrated clinical benefit in patients with the MS or T2DM.[28–30] Subgroup analysis of the 5-year Helsinki Heart Study of patients without prior CHD suggested that diabetic patients who received gemfibrozil (n=135) had a lower incidence of CHD than those who received placebo (3.4% vs 10.5%, respectively; P=.19).[28] The effectiveness of gemfibrozil in the secondary prevention of CVD was demonstrated in the 5-year Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) of men with CHD, low HDL-C, and normal LDL-C.[7] In diabetic patients (n=627), gemfibrozil reduced the composite end point of CHD death, stroke, or myocardial infarction (MI) vs placebo by 32% (P=.004),[29] compared with a reduction of 24% (P<.001) in the total population.[7]

In the 5-year Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study of 9795 diabetic patients (22% of whom had existing CVD while 72% met the NCEP ATP III definition of MS),[30] a nonsignificant reduction in the combined end point of CHD death and nonfatal CHD was observed with fenofibrate (HR, 0.89; P=.16 vs placebo).[6] However, a similar reduction in total cardiovascular events (a secondary end point with a greater number of events) was borderline statistically significant (HR, 0.89; P=.035). Importantly, the low event rate in FIELD (just over 1% per year for the primary end point) may have affected the outcome. Additionally, more patients receiving placebo initiated other lipid therapy, mainly statins (18% vs 8% for fenofibrate patients; P<.001), which may have attenuated the effect of fenofibrate.[6] On the other hand, both serum creatinine and homocysteine levels increased in the patients taking fenofibrate in FIELD, and these changes may have had a negative impact on the outcomes observed.[6] While another trial of diabetic patients (n=418)[31] showed that fenofibrate significantly reduced the progression of coronary atherosclerosis compared with placebo, the sample size was too small to permit conclusions regarding clinical outcomes.

Finally, a post hoc analysis of 1470 patients with MS in the Bezafibrate Infarction Prevention (BIP) study[32] showed that the reduction in any MI and nonfatal MI with bezafibrate was significantly greater than that of placebo (P=.02).[33]

Niacin

Evidence that niacin increases insulin resistance[9,34] has raised concerns about its use in patients with MS or diabetes. However, in a post hoc analysis of the Coronary Drug Project, which included 659 patients with NCEP-defined MS, niacin-treated patients with or without MS had similar relative reductions in the incidence of nonfatal MI and all-cause mortality (HR, 0.86 for both groups).[35] Similarly, in an analysis of subgroups defined by glycemic status (n=1119), niacin produced similar relative reductions in the risk of MI at 6 years, CHD deaths or MI at 6 years, and all-cause mortality at 15 years, at all levels of baseline fasting glucose and at all levels of changes of 1-hour glucose levels from baseline to 1 year.[36]

In the Arterial Disease Multiple Intervention Trial (ADMIT), niacin 3000 mg/d (or the maximum tolerated dosage) decreased triglycerides in patients with and without diabetes by 23% and 28%, respectively, and significantly increased HDL-C by 29% in both subgroups (P<.001 vs placebo for all parameters).[8] Similarly, in the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT) of patients with diabetic dyslipidemia, 1000 or 1500 mg/d of extended-release niacin increased HDL-C by 19% and 24% (P<.05 vs placebo for both doses) and reduced triglycerides by 13% and 28%, respectively (P<.05 vs placebo for the 1500 mg dose only).[37] While niacin had a significant effect on glucose levels in the diabetic patients in both studies, changes were minimal, probably due to changes in diabetes medications.

COMBINATION THERAPIES: THE FUTURE FOR ATHEROGENIC DYSLIPIDEMIA?

Based on the monotherapy studies described above, therapeutic combinations that add triglyceride-lowering and HDL-C–raising effects to statin-induced LDL-C–lowering would seem to be a particularly efficacious approach for patients with MS or T2DM. The most commonly used combinations of existing drugs are statin-fibrate and statin-niacin regimens.

Combinations of Statins and Fibrates

While no studies to date have directly evaluated whether fibrates can further reduce CHD or CVD in statin-treated patients, the efficacy of this combination for altering lipid levels has been investigated. In 120 non-CHD patients with T2DM, combination atorvastatin 20 mg/d and fenofibrate 200 mg/d produced significantly greater changes from baseline in LDL-C (−46%), triglycerides (−50%), and HDL-C (+22%) than those receiving either drug alone (P<.0001 for all parameters).[38]

Similarly, after 12 weeks in the Simvastatin Plus Fenofibrate for Combined Hyperlipidemia (SAFARI) study, which included 102 diabetic patients, combination simvastatin 20 mg/d and fenofibrate 160 mg/d elicited significantly greater decreases in triglycerides (43% vs 20.1%; $P<.001$) and LDL-C (31.2% vs 25.8%; $P<.001$), and significantly greater increases in HDL-C (18.6% vs 9.7%; $P<.001$) than simvastatin alone.[39]

Despite their potential benefits, statin-fibrate combinations may increase adverse effects associated with statin drugs, notably myopathy and liver function abnormalities. By affecting their pharmacokinetics, gemfibrozil appears to increase circulating levels of all statins, except pravastatin, while fenofibrate appears not to interact significantly with simvastatin, pravastatin, or rosuvastatin (atorvastatin was not studied).[40] Evidence suggests that the risk of muscle injury with statins is increased by concomitant gemfibrozil therapy,[41] while the evidence with fenofibrate is less conclusive.[41] Therefore, the choice of which fibrate (either gemfibrozil or fenofibrate in the United States) to combine with statin therapy is difficult. On the one hand, fenofibrate may be safer than gemfibrozil regarding the risk of myositis or rhabdomyolysis; on the other hand, VA-HIT provides strong evidence for the efficacy of gemfibrozil monotherapy in patients with MS or diabetes, while the FIELD study results are, at best, confusing and disappointing. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study includes an arm, which is a randomized double-blind trial of simvastatin monotherapy vs simvastatin in combination with fenofibrate. The results should be available in 2010.

Combinations of Statins and Niacin

Data suggest that the combination of a statin with niacin can reduce cardiovascular events and atherosclerosis.[42,43] In the HDL Atherosclerosis Treatment Study (HATS), diabetic patients receiving simvastatin and niacin had a substantially lower frequency of a first cardiovascular event than placebo-treated patients (3% vs 24%; $P=.04$).[42] However, these data have limitations including small sample size, relatively small number of events, and the comparison of simvastatin/niacin with double placebos rather than simvastatin monotherapy. Simvastatin/niacin treatment also increased glucose and insulin levels.[9]

While the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study, which included 85 patients with MS and 46 with T2DM, reported significantly increased carotid intima-media thickness from baseline (a surrogate marker of CHD) after 12 months with statin plus placebo, but not with statin plus niacin, the differences were not statistically significant across the 2 groups ($P=.08$ for inter-group change).[43] Two large secondary prevention trials of niacin therapy on a background of statins have recently begun and will enroll significant numbers of patients with either MS or diabetes.

Combinations of Statins and *n*-3 (Omega-3) Fatty Acids

Combining statins with *n*-3 (omega-3) fatty acids may prove effective for patients with MS or T2DM. In trials, *n*-3 fatty acids as monotherapy decreased triglycerides in patients with hypertriglyceridemia.[44,45] In a recent study, *n*-3 fatty acids significantly reduced non-HDL cholesterol in hypertriglyceridemic patients already treated with a statin.[46] In the open-label Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico–Prevenzione (GISSI-Prevenzione), treatment with *n*-3 fatty acids significantly decreased the RR of the combined primary end point of death, nonfatal MI, and stroke by 10% ($P=.048$) in 2836 patients with recent ($\leq$3 months) MI.[47] Additionally, the results of a metaanalysis suggest that intake of omega-3 polyunsaturated fatty acids may reduce overall mortality, mortality due to MI, and sudden death in CHD patients.[48] In the recent Japan EPA Lipid Intervention Study (JELIS), patients receiving 1800 mg/d of eicosapentaenoic acid experienced a 19% relative reduction in major coronary events compared with statin-treated controls (2.8% vs 3.5%; $P=.011$) at mean follow-up of 4.6 years.[49] Unfortunately, as this was not a placebo-controlled trial, the benefit may have been overstated.

NOVEL APPROACHES TO RAISE HDL-C

Statins and either fibrates or niacin are effective at reducing LDL-C and triglycerides, respectively, but substantial increases in HDL-C remain an unreached goal. Niacin is the best agent, but the typical 25% increase often obtained leaves most patients short of normal HDL-C levels.[50] As a result, several approaches are under investigation for achieving much greater increases in HDL-C and/or increasing its function as the vehicle for reverse cholesterol transport. These include intravenous infusions of native apoA-I or the variant apoA-I Milano,[51] orally administered apoA-I mimetics,[52] and oral inhibitors of cholesteryl ester transfer protein (CETP).[53,54] JTT-705, torcetrapib, and anacetrapib are CETP inhibitors that have

Table. Summary of Lipid Changes With CETP Inhibitors ± Statins in Clinical Trials

Study	Patients	Dose; Duration; N	% Change HDL-C	% Change LDL-C
de Grooth et al.[62a]	Healthy participants with mild hyperlipidemia	Placebo; 4 weeks; n=50	↑3	↓3
		300 mg/d JTT-705; 4 weeks; n=48	↑16[c]	↓5
		600 mg/d JTT-705; 4 weeks; n=47	↑26[d]	↓5
		900 mg/d JTT-705; 4 weeks; n=52	↑34[d]	↓7[b]
Kuivenhoven et al.[63e]	Patients with type II dyslipidemia (LDL-C >160 mg/dL; HDL-C <60 mg/dL)	Placebo; 4 weeks; n=52	0	↑2
		300 mg/d JTT-705; 4 weeks; n=53	↑13[c]	↑1
		600 mg/d JTT-705; 4 weeks; n=47	↑28[c]	↓5[b]
Clark et al.[64f]	Healthy young participants with normal HDL-C (mean group values ranged from 48 to 60 mg/dL)	Placebo; 2 weeks; n=9	↓3	↑9
		10 mg/d Tor; 2 weeks; n=6	↑16[c]	↑9
		30 mg/d Tor; 2 weeks; n=6	↑28[d]	↓14
		60 mg/d Tor; 2 weeks; n=6	↑62[d]	↓11
		120 mg/d Tor; 2 weeks; n=6	↑73[d]	↓21[b]
		120 mg/twice daily Tor; 2 weeks; n=6	↑91[d]	↓42[d]
Brousseau et al.[65g]	Patients (n=19) with low HDL-C (<40 mg/dL)	120 mg/ Tor+20 mg Atorva; 4 weeks; n=9	↑61[d]	↓17[b]
		120 mg/d Tor; 4 weeks; n=10	↑46[c]	↓8
		120 mg/bid Tor; 8 weeks; n=6	↑106[d]	↓17
Davidson et al.; McKenney et al.[66,67h]	Patients with below average HDL-C (men <44 mg/dL; women <54 mg/dL)	60 mg/d Tor; 8 weeks; n=34	↑45[c]	↓8
		90 mg/d Tor; 8 weeks; n=33	↑55[c]	↓17[b]
		60 mg/d Tor+20 mg Atorva; 8 weeks; n=31	↑33[c]	↓16[b]
		90 mg/d Tor+20 mg Atorva; 8 weeks; n=32	↑40[c]	↓19[b]
Krishna et al.[57i]	Patients with dyslipidemia (LDL-C 100–190 mg/dL)	Placebo; 4 weeks; n=10	0	↑3
		10 mg/d Ana; 4 weeks; n=10	↑41[b]	↓5
		40 mg/d Ana; 4 weeks; n=9	↑80[c]	↓31[c]
		150 mg/d Ana; 4 weeks; n=10	↑104[c]	↓34[c]
		300 mg/d Ana; 4 weeks; n=10	↑129[c]	↓38[c]

Abbreviations: Ana, anacetrapib; Atorva, atorvastatin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Tor, torcetrapib. [a]For each treatment group, % changes in HDL-C and LDL-C are expressed relative to baseline. [b]$P \leq .01$, [c]$P \leq .001$, [d]$P < .0001$. [e]On a background of pravastatin 40 mg/d. % Changes in HDL-C and LDL-C are expressed as the mean of individual % changes relative to baseline. [a]$P = .03$, [b]$P < .001$. [f]% Changes in HDL-C and LDL-C are expressed as the mean of individual % changes (n=6/group) relative to baseline. [b]$P < .05$, [c]$P < .01$, [d]$P < 001$. [g]% Changes in HDL-C and LDL-C for the torcetrapib + atorvastatin group are those achieved by torcetrapib beyond those of atorvastatin alone. A subgroup of 6 subjects not receiving atorvastatin also received 120 mg torcetrapib twice daily for 4 more weeks. [b]$P = .02$, [c]$P = .001$, [d]$P < .001$. [h]% Changes in HDL-C and LDL-C are from baseline to the end of week 8 and relative to placebo. [b]$P < .01$, [c]$P \leq .0001$. [i]% Changes in HDL-C and LDL-C are from baseline to the end of week 4.[b]$P = .0039$, [c]$P < .0001$. Reproduced with permission from Clark.[53]

demonstrated a capacity to substantially increase HDL-C levels in preclinical and clinical studies (Table).[55–57]

Given the proven benefit of potent LDL-C–lowering with statin therapy and the substantial elevations in HDL-C seen with experimental CETP inhibitors, the combination of these 2 classes of therapy would appear to offer potential benefits for the treatment of patients with atherogenic dyslipidemia (Table). Yet, despite the promising findings from lipid efficacy studies, the clinical development of CETP inhibitors is proceeding with caution. Recently, it was apparent from 3 randomized, 2-year, surrogate end point trials (Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor 1 and 2 [RADIANCE 1 and 2], and Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation [ILLUSTRATE]) that torcetrapib/atorvastatin combination therapy had no significant beneficial impact on atherosclerotic progression vs atorvastatin alone, despite substantially increasing HDL-C and reducing LDL-C levels.[58–60] Torcetrapib was

associated with a significant increase in blood pressure (BP) in these studies. The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, a very large, phase 3 cardiovascular end point trial with torcetrapib (n=15,067), which was running concurrently with the surrogate end point trials, was halted after the independent Data and Safety Monitoring Board found a statistically significant imbalance in all-cause mortality between patients receiving torcetrapib/atorvastatin and those receiving atorvastatin alone after <2 years of follow-up.[61] Possible explanations for this outcome include off-target effects of torcetrapib itself or adverse effects due to CETP inhibition. BP increased in ILLUMINATE; however, exploratory post hoc analyses have not suggested that the increased risk of death was associated with adverse changes in the levels of BP, potassium, sodium, and bicarbonate in torcetrapib-treated patients. The possibility that CETP inhibition generated dysfunctional HDL particles cannot be excluded. Neither of the 2 CETP inhibitors in development (JTT-705 and anacetrapib) raises BP and therefore may not be associated with similar adverse effects. However, until these or other new CETP inhibitors are evaluated in long-term trials for safety and efficacy, the concept of raising HDL to achieve atheroprotection using this class of drugs remains a hypothetical one.

SUMMARY

The prevalence of MS and T2DM mellitus is increasing globally, largely as a consequence of the obesity pandemic. Among the several factors that define MS is a characteristic atherogenic lipid profile. This same dyslipidemia characterizes T2DM, and in both cases, the lipid disorder contributes to the increased risk for CVD in these individuals. Current guidelines for the management of atherogenic dyslipidemia recommend lowering LDL-C to evidence-based target levels, with a subsequent focus on elevating HDL-C levels and reducing triglyceride levels. Statins effectively reduce LDL-C levels and are proven to reduce the risk of clinical cardiovascular events. However, additional intervention is required in order to reduce the risk of CVD further. Based on epidemiologic data and some monotherapy trials, both triglycerides and HDL are attractive therapeutic targets. However, there are few studies in which combinations of statins and other lipid-altering agents have been compared with statin therapy alone. Additionally, although triglycerides can be reduced substantially by several of the available agents, these same agents have a limited ability to raise HDL-C. The disappointing results from the recent phase 3 clinical trials with the CETP inhibitor torcetrapib raise concerns about the future of that approach to HDL-raising therapy. Important trials comparing statin monotherapy with statin plus fibrate or niacin are underway.

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