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Editorial Articles

# Is lower and lower better and better? A re-evaluation of the evidence from the Cholesterol Treatment Trialists' Collaboration meta-analysis for low-density lipoprotein lowering

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**Abstract:** Researchers from the Cholesterol Treatment Trialists' (CTT) Collaboration have argued for maximal lowering of low-density lipoprotein cholesterol (LDL-C) by the use of pharmacologic agents, with the strongest evidence coming from the five comparison statin studies in their second meta-analysis. The CTT meta-analysis has many strengths but also a number of limitations, which have not been discussed and which, given the clinical implications, require consideration. Among these are: (1) the impact and validity of including revascularizations within a composite primary end point; (2) the inclusion of the A-Z study, whose design does not allow for valid comparisons of two statin regimens; (3) the fact that baseline LDL-C levels in the comparison studies were not low enough to test whether statin therapy reduces risk significantly in groups with an initial low LDL-C; and, most important, (4) authors of the five studies compared doses at the extremes of statin regimens. However, the clinical choice is not between the lowest and the greatest dose of a statin statin regimens, for example, between 10 and 80 mg atorvastatin, but, more realistically, between intermediate and high dose, that is, between 40 and 80 mg atorvastatin. On the basis of the CTT meta-analysis, we calculate that any potential gain from increasing the dose from 40 to 80 mg atorvastatin would be very small, at best a further 2% further reduction in clinical events. The increase in dose, unfortunately, would likely be associated with increased side effects and decreased compliance. Accordingly, whether net benefit would be demonstrable cannot be assumed. It follows that definitive evidence supporting maximal lowering of LDL-C or maximal dose of statins is still lacking and guidelines, if they are to be evidence-based, should acknowledge this uncertainty.


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Statin therapy has substantially improved clinical outcomes in patients with symptomatic cardiovascular disease and in subjects at high risk of cardiovascular events. The question that naturally follows is whether there is a limit to the extent to which low-density lipoprotein (LDL) should be lowered To be clear, the question is not whether lower is better but whether lower and lower is better and better? In 2005, a supplementary report from Adult Treatment Panel III[1] recommended that a target for LDL cholesterol (LDL-C) of <1.8 mmol/L (70 mg/dL) "should be considered for very high-risk patients." Since then, the recommendation has been strengthened to become virtually routine whereas the target population has been extended to any high-risk patients and beyond and has been adopted by a number guideline groups, including most recently the European Society of Cardiology and the European Atherosclerosis Society.[2] The question whether lower and lower is better and better has practical and economic significance, not simply for the future of agents that already exist but also for newer classes of pharmacologic therapies such as the proprotein convertase subtilisin/kexin type 9 (ie, PCSK9) inhibitors and, to the extent they might achieve benefit through lowering LDL, the cholesteryl ester transfer protein inhibitors. It is also imperative that the evidence be evaluated critically to optimally inform future guidelines and policy decisions.

The strongest evidence for this position comes from the results of the Cholesterol Treatment Trialists (CTT) meta-analyses. In the first of these, which assembled data from 14 studies and 90,056 subjects,[3] researchers concluded there was strong evidence for a constant benefit, a decrease of 20% in clinical events per mmol/L lowering of LDL-C. The second extended the number of trials to 26, the number of subjects to 170,000, and reaffirmed the conclusions of the first. The five randomized clinical trials that tested the hypothesis that more potent statin therapy produces a superior clinical outcome than less potent statin therapy[4–8] were the principal addition and the principal focus of the second meta-analysis.[9] On the basis of the totality of their findings, CTT[9] recommended further lowering of LDL-C in high-risk subjects who have already reached an LDL-C of <70 mg/dL to be achieved, if necessary, either with 80 mg of atorvastatin or 20 mg of rosuvastatin or a generic statin in combination with other LDL-C–lowering therapies.

Hayward and Krumholz[10] have pointed out, however, that the statin studies were not designed to achieve a specific target level and, with the exception of the TNT (Treat to New Targets),[4] Post-CABG,[11] and GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation),[12] they are correct. Thus, overall, the statin clinical trials are tests of therapies, not tests of treatment targets. Moreover, these authors note that one should not assume that all the benefits of statins relate to LDL lowering. Nevertheless, Robinson et al[13] have shown that the benefits of LDL-C lowering are very similar irrespective of the modality of treatment.

In addition, and also not widely appreciated, is that an LDL-C of 1.8 mmol/L (70 mg/dL) corresponds to the 8th percentile of the American population.[14] On a population basis, this is an extremely low level. As enthusiasm grows for even lower levels of LDL-C for even larger numbers of people, the reality of how great a task it will be to achieve such targets needs to be considered. Accordingly, a closer review of the CTT meta-analysis, and in particular, the results of the five comparison studies, seemed warranted.

## The CTT meta-analysis

The many strengths of the CTT meta-analysis[9] must be acknowledged. Data from all the major comparison statin dose studies have been included, and the extent of the data from the 21 statin versus placebo studies is impressive by any measure. This is an individual patient-level analysis of 170,000 patients, and the authors are widely regarded as experienced and expert in meta-analyses. Moreover, broader, and therefore, more stringent confidence intervals were chosen compared with the original studies (99% vs 95%) to compensate for comparisons of multiple subgroups. There was a highly significant 13% (95% confidence interval [95% CI] 7%–19%) reduction in major coronary events (2.2% vs 1.9% per year, $P < .0001$) and an even greater 19% (95% CI 15–24, $P < .001$) reduction in coronary revascularization (3.2% vs 2.6%). Additional analyses demonstrate that the degree of benefit between the lower- versus higher-dose arms of the statin comparison studies is consistent with the degree of benefit observed in the statin versus placebo studies. These analyses are determined by the extrapolation of the observed differences in the trials assuming a uniform 20% reduction in events per 1 mmol/L LDL-C reduction. Finally, benefit is observed in many subgroups of participants. The many obvious strengths of the CTT meta-analysis have led to widespread acceptance of their conclusions.

## Limitations of the CTT meta-analysis

As with any study, there are also limitations. Because they have received less attention than the strengths of the CTT meta-analysis, they will be our focus. Investigators from the CTT state that further lowering of LDL-C will produce further substantial clinical benefit even if LDL-C levels are already low. That is the contention we will examine.

### Absolute benefit depends on which end point is chosen

The primary end point in the second CTT meta-analysis is a composite of coronary deaths, nonfatal myocardial infarctions, ischemic strokes, and revascularizations 30 days or more after randomization. Revascularizations are the least "hard" of the end points that can be included in a composite cardiovascular outcome because the indications for the procedures are difficult to document and do not bear as clear an impact on events such as death and heart failure

as does myocardial infarction. Moreover, for the end point of revascularization, there appears to be significant heterogeneity on the basis of study design. Thus, in the CCT-meta-analysis,[9] the proportional reduction in revascularization rate per mmol/L reduction in LDL-C was significantly greater in the 5 comparison studies than in the studies of placebo versus control (34%, 95% CI 27–40 vs 24%, 95% CI 20–27, $P = .01$).

The inclusion of revascularization more than doubles the absolute event rate and therefore more than doubles the absolute benefit per mmol/L of lowering of LDL-C. Thus, the extent of benefit depends on the definition of benefit, a point practicing physicians and policymakers should keep in mind. Finally, a composite clinical outcome was not identified prospectively as an end point in the original CTT protocol,[15] and therefore, any analysis based on a composite outcome as a primary end point is a *post facto* analysis based on an *a posteriori* hypothesis, which must diminish the *a priori* validity of the results.

## The A-Z trial was not designed to compare two intensities of LDL lowering and should not have been included in the CTT meta-analysis

The A-Z trial[8] was designed to test two approaches to therapy, not two regimens of statin therapy and, therefore, should not be included in the meta-analysis. In one arm of the A-Z trial, subjects were on placebo for the first 4 months and were then treated with 20 mg of simvastatin whereas, in the other, subjects were started immediately on 40 mg of simvastatin, which was increased to 80 mg simvastatin after 1 month. The total duration of follow up was 24 months. This means that the placebo/20 mg simvastatin subjects were followed for 24 months but were only treated for 20, whereas the 40/80 mg simvastatin subjects were followed, and treated, for 24 months. The period of treatment is, therefore 17% longer in the 80-mg atorvastatin group compared with the 20-mg simvastatin group.

For a randomized controlled trial to yield valid results, not only must all subjects be assigned randomly to the experimental groups, but also, except for the experimental intervention, the follow-up and management of all subjects must be identical. This was not the case in the A-Z study.[8] Accordingly, pooling the results of this study with the others is very questionable. Nor, unfortunately, is there any way to make a post facto adjustment of the periods of follow-up without making arbitrary post facto changes in data analysis. Indeed, anatomic disease progression during the 4 months of no treatment may only produce an event after this time period. The CCT protocol stipulates that potentially eligible studies must be unconfounded, involve $\geq$500 patients, and last $\geq$2 years.[15] In our view, the unequal periods of follow-up are a strong confounder for A-Z and, therefore, we question the appropriateness of including this trial in this meta-analysis.

If A-Z is removed, that leaves only four trials, in which one, the TNT study,[4] investigators reported a 22% benefit for an LDL-C difference of 0.62 mmol/L (24 mg/dL) versus an average 25% benefit for a reduction of LDL-C of 1 mmol/L (38.5 mg/dL) calculated by the CCT.[9] The benefit in TNT was, therefore, approximately 54% greater than predicted by the CCT study, suggesting this trial may be an outlier. It is, of course, perfectly valid to include TNT in the meta-analysis but, as the number of studies becomes fewer, the influence of a potential outlier on the remaining three becomes greater. It is also worth noting that if pretreatment characteristics such as age, body mass index, hypertension, apoB and apoA-I, but not lipids, are taken into account in the TNT study, on-treatment levels of LDL- LDL-C, non–high-density lipoprotein (non-HDL-C) and apoB- no longer predict residual risk.[16] This finding that pretreatment characteristics determine outcome does not appear to be consistent with the model of a constant benefit per LDL lowering.

## How secure is the conclusion that the percent reduction of clinical benefits by statin is independent of the level of LDL-C?

The critical test of the lower and lower is better and better hypothesis is that reductions of levels of LDL-C that are already low will produce significant clinical benefit in populations that are at high absolute risk. Although this hypothesis may be correct, there is no strong evidence in its favor from the five comparison studies for the simple reason that these studies did not include sufficient numbers of subjects with low LDL-C at entry. The lowest average baseline LDL-C of the subjects enrolled in any of these trials was 2.57 mmol/L (106 mg/dL) in the PROVE-IT TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) study, but approximately 25% of these subjects were sampled while on statin therapy.[5] Moreover, in the PROVE-IT TIMI 22 study, irrespective of the treatment regimen, subjects with an LDL-C $>$3.25 mmol/L (125 mg/dL) had significant benefit, whereas those with an LDL-C $<$3.25 mmol/L did not, a result, which does not support the lower is better hypothesis. The average LDL-C levels were 2.88 mmol/L (111 mg/dL) off statin in the A-Z trial,[8] but there was no evidence of significant benefit for the more intensive regimen. In SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine)[7] and TNT,[4] the baseline levels recorded in the published studies represent the levels after a run-in period of treatment with the lower-dose statin therapy. Thus, in the TNT trial, the mean baseline LDL-C was 2.55 mmol/L (98 mg/dL), but this value was on treatment with 10 mg of atorvastatin. The actual pretreatment level was 3.95 mmol/L (152 mg/dL).

However, authors from the Heart Protection Study[17] noted that subjects enrolled with an LDL-C $<$2.5 mmol/L (97 mg/dL), which was reduced to 1.7 mmol/L (65 mg/dL) by simvastatin, experienced a risk reduction, which was stated to be "about as great" as that in those with greater levels of LDL-C. The limitation here is that the

direct assay used in HPS appeared to underestimate LDL-C by at least 0.39 mmol/L (15 mg/dL) compared with an LDL-C calculated by Friedewald, the measure of LDL-C in most of the clinical trials.[18]

A recent meta-analysis of statin trials[19] reported that the HRs for LDL-C, non-HDL-C, and apoB were virtually identical. The key point for this discussion, however, is that all three were substantially lower than in prospective observational studies,[20,21] which suggests that at low levels, the LDL-attributable risk is low. Moreover, as already noted, in TNT,[16] once pretreatment factors were taken into account, none of the on-treatment values of the three markers was significantly predictive of risk. Furthermore, in JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin),[22] the on-treatment risks associated with LDL-C diminished once LDL-C was <70 mg/dL, an observation that challenges the extrapolation of the CTT relation between risk and LDL-C lowering. All these observations are consistent with the hypothesis that when LDL is low, the LDL-attributable risk is low. Thus, there do not appear to be an adequate mass of data on the benefit of initiating statin therapy in subjects at high cardiovascular risk but low LDL-C to be confident as to the degree of clinical benefit that will be achieved.

## Is the therapeutic comparison evaluated in the CTT meta-analysis the clinically relevant scenario?

In our view, this is the most significant weakness of the CTT meta-analysis. The comparison studies are characterized as tests of more- versus less-intensive statin regimens whereas, in fact, they are, for the most part, comparisons of a low dose of a statin versus the greatest possible dose of that statin. However, the choice for physicians is not between prescribing a patient 10 mg of atorvastatin or 80 mg of atorvastatin. The real clinical choice, the one that was not addressed in any of the comparison studies and therefore cannot be addressed in the meta-analysis, is between atorvastatin 40 mg and atorvastatin 80 mg per day, that is, between a moderate and the highest dose of a statin.

This is not a semantic issue. The absolute LDL lowering with statins is greatest with the initial dose of a statin and is directly related to the pretreatment level of LDL-C. This means that the absolute benefit with statin therapy will depend on the initial LDL-C and whether the patient is statin naïve. To determine the maximal potential boundaries of benefit, let us assume that the reduction of LDL-C by 1 mmol/L does reduce clinical events by 20%, just as proposed by CTT.[9] Table 1 lists the changes in LDL-C and risk in a statin-naïve patient with an initial LDL-C of 2.00 mmol/L. If 80 mg of atorvastatin reduces LDL-C by 50%, the 10 mg of atorvastatin will reduce LDL-C by 42% and 40 mg of atorvastatin will reduce LDL-C by 47%. That is, a doubling of statin dose produces only a further 6% lowering of LDL-C. Accordingly, on the basis of the CTT meta-analysis, a difference of dose between 40 mg and 80 mg of atorvastatin would produce only a further 0.06 mmol reduction in LDL-C and therefore only a further reduction of 1.2% in clinical events.

**Table 1** Outcomes in statin-naïve patients with LDL-C 2.00 mmol/L

| Dose of atorvastatin, mg/day | % decrease in LDL-C | LDL-C achieved, mmol/L | Absolute decrease in LDL-C, mmol/L | Predicted decrease in events, % |
|---|---|---|---|---|
| 10 | 42 | 1.16 | 0.84 | 16.8 |
| 20 | 45 | 1.10 | 0.90 | 18.0 |
| 40 | 47 | 1.06 | 0.94 | 18.8 |
| 80 | 50 | 1.00 | 1.00 | 20.0 |

LDL-C, low-density lipoprotein.

For example, if 10,000 subjects with an LDL-C of 2.00 mmol/L and an event rate of 20% over 10 years were treated with 40 mg of atorvastatin, they would be expected to experience 1,624 events, 18.8% less than the 2000 expected without treatment. Treatment with 80 mg for 10 years would reduce the expected number of events to 1600 or 24 fewer events among 10,000 high-risk patients (i.e., 1 event avoided for each 417 patients treated) with the greater dose of atorvastatin. Table 2 lists the changes in LDL-C and risk in a patient with an LDL-C of 2.00 mmol/L who is already taking atorvastatin 10 mg daily. For this much more common situation, increasing the dose of atorvastatin from 40 to 80 mg per day will further reduce events by only 2.1% from 3.4% to 5.5%.

When one uses the same estimates as for the first scenario, with risk remaining at 20% over 10 years even though subjects are already treated with 10 mg of atorvastatin, increasing atorvastatin from 40 mg to 80 mg per day will require treatment of 10,000 subjects to prevent 42 additional events over 10 years. To demonstrate that either of these differences in events truly exists would require an enormous clinical trial, which will never be performed, which means that the benefit must be assumed and will never be convincingly demonstrated. At best, therefore, the overall potential differences by increasing

**Table 2** Outcomes in patients with LDL-C 2.00 mmol/L receiving 10 mg of atorvastatin

| Dose of atorvastatin, mg/day | LDL-C achieved, mmol/L | Absolute decrease in LDL-C, mmol/L | Predicted decrease in events, % |
|---|---|---|---|
| 20 | 1.90 | 0.10 | 2.1 |
| 40 | 1.83 | 0.17 | 3.4 |
| 80 | 1.72 | 0.28 | 5.5 |

LDL, low-density lipoprotein.

**Table 3** Comparison of on-treatment marker general population percentiles for each trial with LDL-C <80 mg/dL

| | Marker levels, mg/dL | | | Marker percentiles, %* | | |
|---|---|---|---|---|---|---|
| RCT | LDL-C | Non-HDL-C | ApoB | LDL-C | Non-HDL-C | ApoB |
| CARDS[30] | 72 | 100 | 80 | 10 | 14 | 24 |
| TNT[4] | 75 | 101 | 91 | 11 | 14 | 39 |
| IDEAL[6] | 79 | 101 | 84 | 14 | 14 | 29 |
| SPARCL[31] | 70 | 92 | 81 | 8 | 9 | 25 |
| JUPITER[32] | 62 | 84 | 71 | 5 | 5 | 13 |
| HPS[17] | 74 | 113 | 84 | 11 | 25 | 29 |
| Mean | 72 | 99 | 82 | 10 | 14† | 26‡ |
| Range | 62–79 | 84–113 | 71–91 | 5–14 | 5–25 | 13–39 |

ApoB, apolipoprotein B; CARDS, Collaborative Atorvastatin Diabetes Stud; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End points through Aggressive Lipid Lowering; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL, low-density lipoprotein; non-HDL-C, non-high-density lipoprotein; RCT, randomized controlled trial; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TNT, Treat to New Targets.

*Calculated from National Health and Nutrition Examination 2005–2008 Surveys (NHANES) data accounting for the complex sample design.[14]

†$P = .138$ vs LDL-C mean percentile by paired $t$-test.

‡$P = .001$ vs LDL-C and $P = .009$ vs non-HDL-C.

from moderate to greatest dose statin would be small and these differences, it must be recalled, are determined by the composite end point, which includes revascularizations, which accounts for just more than one-half of benefit. Moreover, these estimates are best-case scenarios in that they are assume the relation posited by CTT between lowering of LDL-C and decrease in risk does hold in patients with lower levels of LDL-C, an assumption challenged by more recent evidence.[19,16,22]

On the other hand, increased doses of statins will increase side effects. The chance of serious ones, such as rhabdomyolysis and now, it seems, diabetes appears to be low, although more work needs to be done with regard to the risk of diabetes. Nevertheless, serious side effects occur, and the risk of these side-effects, ie, myalgia, rhabdomyolysis, and diabetes, relates, among other factors, to the dose of statins.[23,24] Rhabdomyolysis and diabetes, as side-effects of statins, pose direct threats to health, but are uncommon. Myalgia, by contrast, is very common and, even though not generally considered a major adverse event, it may pose an important indirect threat to health because compliance is reduced and decreased adherence with statin therapy has been associated with increased mortality.[25,26]

Thus, whether there would be net benefit by increasing atorvastatin from 40 mg to 80 mg daily depends on the balance between a small, possible, additional benefit versus probable loss as the result of reduced compliance. The fact is that the five comparison studies were designed to have the greatest chance to show clinical benefit by increasing statin dose and, simply because there is a positive difference in outcome between 10 and 80 mg of atorvastatin does not mean there will be a positive outcome between 40 and 80 or even between 20 and 80 mg of atorvastatin. The comparison statin studies were designed to produce a positive result. Experiments should be designed to test hypotheses, not support them, and meta-analysis cannot overcome design bias.

## An alternate approach

Both the meta-analysis by Boekholdt et al[19] and the Heart Protection Study[17] have demonstrated that the on-treatment HRs of LDL-C, non-HDL-C, and apoB for residual risk are clinically indistinguishable. Does that mean all three predict risk equally in all individuals? Not at all: in at least 30% of individuals, the mass of cholesterol per apoB particles is either substantially greater or less than the norm.[27] In these subjects, the concentrations of LDL-C and/or non-HDL-C relative to apoB or LDL particle number are discordant, that is, the concentrations of LDL-C and non-HDL-C, expressed as population percentiles, are significantly different from the concentration of apoB, expressed as a percentile of the population. Moreover, statins reduce apoB less than LDL or non-HDL-C.[28] The consequence is that on-treatment apoB may be greater, relative to the population, than LDL-C or non-HDL-C. Because risk is related to concentration, this means the risk predicted by apoB would be greater than the risk predicted by LDL-C or non-HDL-C.[29]

That this is commonly the case is illustrated in Table 3,[4,6,14,17,30–32] which lists the average concentrations, as well as the corresponding percentiles for the American population, for LDL-C, non-HDL-C, and apoB in the six statin trials,[4,6,17,31,32] that have achieved an on-treatment LDL-C less than 2 mmol/L. The average on-treatment LDL-C was at the 10th percentile, the average non-HDL-C at the 14th percentile, whereas the average apoB was at the 26th percentile. Moreover, the difference in population percentiles between LDL-C and non-HDL-C was not statistically significant, whereas the differences between apoB and LDL-C and apoB and non-HDL-C were.

These results indicate that, on average, the number of atherogenic particles as determined by apoB was substantially greater than would have been predicted from the

population levels of LDL-C and non-HDL-C and, therefore, that apoB is superior to LDL-C or non-HDL-C to identify the subgroup of individuals who have achieved their LDL-C or non-HDL-C targets but still have levels of atherogenic particles that could be further reduced with clinical benefit.

## Summary

The CTT meta-analysis has strengths but also limitations, the most important of which is that it could not test the option in statin therapy that matters most in clinical practice- intermediate statin doses.[9] This design bias critically limits the clinical utility of their conclusions and, by extension, any meta-analysis as well as any guideline based on them. As demonstrated, an increase from moderate to greatest dose statin can produce, at best, only the possibility of a small therapeutic gain, which must be balanced against the probability of increased side effects and reduced compliance. Without a clinical trial, there can be no certain answer as to whether highest dose statin is clearly superior to moderate dose statin. Nor does it follow that, as recommended by CTT,[9] combination therapy of statin with ezetimibe, a regimen, which will produce the greatest decrease in LDL-C, will actually produce the clinical benefit predicted. In our view, combination therapy should not be approved or recommended as routine therapy until the results of the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) trial[33] are known.

Clinical care is about the individual patient. Meta-analysis is about the responses of groups, and the outcome of the group cannot be assumed to hold for any particular individual within the group because individuals differ in the factors that determine the success or failure of the treatment.[34] The physicians' challenge is to bridge this gap. For the physician, the optimal dose is not necessarily the maximal dose. Rather the optimal dose represents the optimal trade-off between benefit and side effects, the dose at which compliance is likely to be highest, and must be determined on an individual basis.

Much of the authority of the guideline process lays in the claim that the evidence on which their recommendations are based can be objectively catalogued and judged based on their form. According to this view, randomized clinical trials provide much more secure knowledge than observational studies and a meta-analysis of multiple randomized controlled clinical trials represents the highest grade of evidence and therefore the most reliable knowledge. Expert opinion, such as this commentary, counts for little. However, form alone cannot assure the validity of the conclusions of any study. It is the content of the study—the details of the design, conduct and interpretation of a particular study or meta-analysis—that determines its validity and generalizability. It is the responsibility of the clinical reader, in particular, to analyze and interpret, not just assimilate and repeat, the results of any study, a role that is particularly vital with issues that impact individual and public health. Accordingly, given the totality of the evidence, we are not persuaded that the CTT meta-analysis has demonstrated beyond reasonable doubt that lower and lower is necessarily better and better.

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