Aspirin for primary prevention in diabetes mellitus: from the calculation of cardiovascular risk and risk/benefit profile to personalised treatment

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Summary
Type 2 diabetes mellitus is characterised by persistent thromboxane (TX)-dependent platelet activation, regardless of disease duration. Low-dose aspirin, that induces a permanent inactivation of platelet cyclooxygenase (COX)-1, thus inhibiting TXA2 biosynthesis, should be theoretically considered the drug of choice. The most up-to-date meta-analysis of aspirin prophylaxis in this setting, which includes three trials conducted in patients with diabetes and six other trials in which such patients represent a subgroup within a broader population, reported that aspirin is associated with a non-significant decrease in the risk of vascular events, although the limited amount of available data precludes a precise estimate of the effect size. An increasing body of evidence supports the concept that less-than-expected response to aspirin may underlie mechanisms related to residual platelet hyper-reactivity despite anti-platelet treatment, at least in a fraction of patients. Among the proposed mechanisms, the variable turnover rate of the drug target (platelet COX-1) appears to represent the most convincing determinant of the inter-individual variability in aspirin response. This review intends to develop the idea that the understanding of the determinants of less-than-adequate response to aspirin in certain individuals, although not changing the paradigm of the indication to low-dose aspirin prescription in primary prevention, may help identifying, in terms of easily detectable clinical or biochemical characteristics, individuals who would attain inadequate protection from aspirin, and for whom different strategies should be challenged.

Keywords
Antiplatelet agents, diabetes mellitus, aspirin response, prevention

Search strategy
This document is based on a comprehensive review of the available literature. PubMed database was searched through February 2015 for articles in English reporting aspirin use for primary prevention in diabetes mellitus. The following search terms were used: ‘aspirin’, ‘diabetes’, ‘primary prevention’, ‘antiplatelet therapy’, ‘cardiovascular diseases’, ‘prophylaxis’, ‘cardiovascular risk’ and ‘guidelines’. Identified references were hand-searched to locate other potentially useful references. Clinical randomised trials, prospective cohort studies and retrospective analyses were included, as well as meta-analyses; abstracts were excluded.

In the past two decades, preventive care for adults with diabetes declined substantially the rates of diabetes-related complications (acute myocardial infarction (MI), stroke, end-stage renal disease, lower-extremity amputation). However, a large burden of disease persists because of the continued increase in the prevalence of diabetes (1).

The latest American Diabetes Association (ADA) guidelines for prevention and management of diabetes complications, suggest considering aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (2).

Aspirin to prevent initial cardiovascular events in diabetes mellitus: where do we stand?

In general populations without previous cardiovascular disease (CVD), the absolute benefits of antiplatelet prophylaxis are of uncertain value in primary prevention (3), because the balance between vascular events avoided and major bleeds caused by aspirin is substantially uncertain. In a systematic review of six trials including 95,000 individuals, a 12% risk reduction (4) was found, mainly due to a reduction in non-fatal MI, with a non statistically significant net effect on stroke (a reduction in ischaemic stroke and a slight increase in haemorrhagic stroke). Moreover, vascular mortality was not changed by aspirin treatment. Major bleeding (gastrointestinal and extracranial) increased by 0.03% per year. Two updated meta-analyses (5, 6), including three more recent trials POPAPAD (7), JPAD (8), and AAA (9), demonstrated a...
marginally significant reduction in all-cause mortality, not previously shown in the ATT meta-analysis (4). This 5–6% proportional reduction in all-cause mortality (3) would translate into an NNT in excess of 3000 to prevent one (largely nonvascular) death.

Thus, ESC guidelines (10) do not recommend aspirin in primary prevention due to its increased risk of major bleeding. However, the more recent American College of Chest Physicians guidelines (11) suggest low-dose aspirin over no aspirin therapy for persons aged 50 or older without symptomatic cardiovascular disease, with no emphasis on patient characteristics, such as older age, sex, or diabetes mellitus.

A meta-analysis of 102 prospective studies including about 700,000 people found about a two-fold excess risk for vascular diseases in patients with diabetes mellitus (12). Thus, although the dogma of diabetes as a coronary heart disease equivalent (13) has gradually waned, also due to the absolute risk reduction exerted by concurrent treatment with disease modifying drugs, such as anti-diabetic, blood pressure and lipid lowering drugs, diabetes is still a major cardiovascular risk factor. Considering that type-2 diabetes mellitus (T2DM) is characterised by persistent thromboxane-dependent platelet activation (14–16), low-dose aspirin, that induces in platelets a permanent inactivation of cyclooxygenase (COX)-1, thus inhibiting the biosynthesis of thromboxane (TX) A₂, should be theoretically considered as the drug of choice. But, the only rationale for using a treatment is that it is effective, and no randomised evidence until now has drawn definite conclusions.

Low-dose aspirin is effective in secondary prevention of cardiovascular disease in patients with DM who experienced a previous vascular event (17). A low dose of aspirin (75 to 150 mg/day) was found to be at least as effective as higher daily doses, and bleeding complications were reduced with lower doses. In a large meta-analysis of secondary prevention trials performed by the Anti-thrombotic Trialists’ Collaboration (18) the incidence of vascular events was reduced from 22.3% to 18.5% in the cohort of DM patients (p<0.002) and from 16.4% to 12.8% (p<0.00001) in non-DM patients. Thus, there is no apparent reason to treat patients with DM and CVD differently from non-DM patients and low-dose aspirin is recommended for secondary prevention of ischemic syndromes (17).

For primary prevention of CVD events in adults with diabetes, the most recent ACCF/AHA guidelines (19) recommend low-dose aspirin in people who are at increased CVD risk (10 year risk of CVD events over 10%) and who are not at increased risk of bleeding. Low-dose aspirin might be considered for those with diabetes at intermediate CVD risk; whereas aspirin is not recommended for diabetic patients with low CVD risk (10-year CVD risk under 5%) as the potential adverse effects from bleeding offset the potential benefits. Consistent with this uncertainty, antiplatelet therapy with aspirin in adults at a low CVD risk is not recommended by the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on CVD Prevention in Clinical Practice (20).

However, direct evidence of its efficacy and safety in the diabetic setting is lacking or, at best, inconclusive. An individual patient-level meta-analysis by the ATT Collaboration showed a similar effect of aspirin on major cardiovascular events in individuals with and without diabetes (risk ratio [RR]: 0.88 [95% confidence interval (CI): 0.67 to 1.15] and 0.87 [95% CI: 0.79 to 0.96], respectively) (8), with a wider 95% CI for diabetes attributable to its smaller representation (4,000 diabetic vs. about 91,000 without diabetes) (4). Conversely, in the most up-to-date meta-analysis, which includes three trials conducted specifically in patients with diabetes and six other trials in which such patients represent a subgroup within a broader population, aspirin was found to be associated with a non-significant 9% decrease in the risk of coronary events (RR 0.91; 95% CI 0.79–1.05) and a non significant 15% reduction in the risk of stroke (RR 0.85; 95% CI 0.66–1.11). These results have been interpreted as suggesting that aspirin probably produces a modest reduction in the risk of cardiovascular events, but the limited amount of available data precludes a precise estimate of the effect size (21).

Probably, the large heterogeneity of the nine primary prevention studies, which include only three trials specifically designed to assess aspirin effect in diabetes mellitus, may help to explain the inconclusive results (3). In fact, they addressed widely different populations at-risk subjects, giving different aspirin regimens, with low event rates, thus they were underpowered to demonstrate a benefit in their primary endpoint, despite their large sample size and extended follow-up. Moreover, these trials presented a high rate of aspirin discontinuation during the follow-up, were performed before statin era or statin treatment prevalence was not reported, and with really different primary endpoints (from as hard as mortality to as soft as a mix of atherosclerotic events). Thus, the results of meta-analyses of these trials have been over-interpreted as providing proof of efficacy of low-dose aspirin in primary prevention, rather than generating hypotheses on a realistic effect size to be tested in properly sized randomised trials (3).

Finally, we would emphasise that T2DM is associated with increased risk for some cancers (particularly, pancreas and colorectal) (22). Interestingly, long-term follow-up of randomised trials of aspirin in primary cardiovascular prevention showed that low-dose aspirin reduces colorectal cancer incidence and mortality from five years onwards (23, 24). However, in the Rothwell’s meta-analyses, data on cancer prevention by aspirin in diabetic patients are still lacking. Clearly, a reduction in overall cancer incidence from prophylactic aspirin treatment in diabetes mellitus, would tilt the balance of benefits and risks, and thus broaden the indication for treatment in this population.

Identification of clinical characteristics of patients with increased platelet reactivity for a personalised therapy

Lower-than-expected efficacy of aspirin and higher-than-expected safety: do they reflect inability of aspirin to suppress platelet function?

Recently, a population-based study analysing data from 4.1 million individuals in Italy, with and without diabetes, concluded that aspirin therapy is associated with an excess on both gastrointestinal and intracranial bleeding in nondiabetic subjects, but only
slightly increased the risk of bleeding in patients with diabetes (RR 1.09, 95% CI 0.97–1.22), suggesting that these data might provide indirect evidence that the efficacy of aspirin to suppress platelet function is reduced in these patients (25).

The observational and randomised evidence about the safety of low-dose aspirin in patients with diabetes is inconclusive. Even in the large meta-analysis by Pignone et al. (19) the risk of bleeding was not reported, and in the ATT meta-analysis too few major bleeding events occurred in patients with diabetes to estimate the effect of aspirin reliably (26). Given the paucity of data in support of the hypothesis raised by the mentioned observational study (25), we should consider that the risks of aspirin in diabetic individuals are comparable to those of patients without diabetes, until additional data on the safety of low-dose aspirin in diabetes become available. Therefore, the balance of benefits and risks of aspirin in primary prevention is far less clear than in secondary prevention; further data from randomised trials of individuals at intermediate cardiovascular risk are needed. Two trials adequately sized and specifically designed in diabetes (3) are currently underway and are expected to address unanswered issues: A Study of Cardiovascular Events in Diabetes (ASCEND) (27) and A Combination of aspirin and simvastatin for Cardiovascular Events Prevention in Diabetes (ACCEPT-D) (28). Both trials are enrolling patients with T1 or T2DM, free of vascular disease. Ongoing trials are anticipated to clarify whether and for whom antiplatelet therapy is effective in preventing major cardiovascular events (29).

Mechanistic basic biology vs hard, and clinically important, outcomes

Although possible sources of bias which might have affected the results of clinical trials of aspirin in diabetes cannot be ruled-out, an increasing body of evidence supports the concept that less-than-expected response to aspirin may underlie patho-physiological mechanisms related to residual platelet hyper-reactivity despite anti-platelet treatment at least in a fraction of the diabetic population. The first pivotal question is whether there is evidence that the inhibitory effect of low-dose aspirin on platelet function is modified in the presence of diabetes, and whether this applies to all diabetic persons. The second question is whether methods used to assess platelet inhibition by aspirin are accurate and reliable. The third and consequential question is how to identify, in terms of easily detectable clinical or biochemical characteristics, individuals who would gain inadequate response to aspirin, if any.

A large body of experimental and clinical evidence supports the hypothesis of an inter-individual variability in the response to aspirin, previously and incorrectly referred to as “aspirin resistance”. Awareness of the largely unreliable nature of functional methods used to measure the response to aspirin (30) has substantially debunked this phenomenon. The various methods used to quantify the antiplatelet effect of aspirin in these studies poorly reflect the biochemical pathway affected by aspirin, i.e. platelet COX-1 activity (31) and variably reflect the aspirin-sensitive TX-dependent component of platelet aggregation (32), whereas the impact of potential non-COX-1 effects of aspirin are still of unclear significance (33). Moreover, different platelet function assays correlate poorly among each other (34). In addition, characterisation of “resistant” versus “responder” status is typically based on a single determination of platelet function, with the underlying assumption that this determination represents a stable phenotype.

In contrast, serum TXB$_2$ and urinary 11-dehydro-TXB$_2$, provide reliable information on the maximal biosynthetic capacity of circulating platelets ex vivo and on the actual rate of TXA$_2$ biosynthesis in vivo, respectively (32). Less than-complete inhibition of platelet TXA$_2$ production and TXA$_2$-dependent platelet activation as assessed by these methods is a more reliable, mechanism-of-action-based, tool to assess aspirin responsiveness.

Multiple mechanisms of variable response to aspirin can be speculated (Figure 1), but several of them remain somewhat speculative and not yet proven in the clinical practice. Apart the questionable relevance of COX-1 polymorphisms (35) as determinant of less-than-expected response to aspirin, all these mechanisms appear potentially modifiable. Upstream any of them, compliance should be assessed, also by pill count, to exclude that poor adherence to antiplatelet treatments, as well to other disease-modifying drugs, may be incorrectly diagnosed as suboptimal response in patients with multiple drug prescriptions (36).

Aspirin pharmacokinetics may be affected by a larger distribution volume, due to excess fat. In this regard, aspirin formulation (i.e. enteric-coating) and dosage may be critical issues further affecting aspirin bioavailability (37). Consistently, weight loss and avoidance of enteric-coated formulations may restore adequate bioavailability and improve the efficacy of aspirin. On the other hand, the use of enteric-coated aspirin has been introduced to spare prostacyclin formation and to reduce gastrointestinal side effects, since the long-term administration of low doses of conventionally formulated aspirin has been shown to depress the biosynthesis of prostacyclin (38), as well as the homeostatic increase in prostacyclin biosynthesis during TXA$_2$ inhibition, as a mechanism of thrombore sistence (39).

Lower response to aspirin may be related to the enhanced platelet turnover in DM, through increased reactivity of younger platelets, increased platelet COX-2 expression, or incomplete inhibition of COX-1 (Figure 1). Furthermore, oxidative stress-mediated mechanisms may be associated with suboptimal response to aspirin, as reviewed elsewhere (40). These include: 1) mechanisms counteracting the antiplatelet effect of aspirin, such as reduced platelet sensitivity to the antiaggregating effects of nitric oxide, due to high glucose-mediated oxidative stress; 2) mechanisms interfering with COX acetylation especially at platelet level, e.g. lipid hydroperoxide-dependent impaired acetylating effects of aspirin; 3) mechanisms favouring platelet priming (lipid hydroperoxides) or activation (F$_2$-isoprostanes, acting as partial agonists of thromboxane receptor), or aldose-reductase pathway-mediated oxidative stress, leading to enhanced platelet TXA$_2$ generation or TX receptor activation); 4) mechanisms favouring platelet recruitment, such as aspirin-induced platelet isoprostane formation). Among these, enhanced platelet isoprostane formation, as observed in diabetic subjects, has emerged as a potentially important factor that would counterbalance the inhibition of TXA$_2$, therefore hampering
the antiplatelet effect of aspirin (41) (Figure 1). Indeed, aspirin-treated diabetic patients showed platelet TxB₂ inhibition but higher isoprostanes production three and seven days after aspirin administration, compared with non-aspirin-treated diabetic patients, concurrent with enhanced platelet reactive oxygen species (ROS) formation and NADPH oxidase 2 (NOX2) activation, suggesting a cause-and-effect relationship between NOX2-generated ROS and platelet isoprostane overproduction (41). While aspirin alone was associated with NOX2 up-regulation and isoprostane over-production, addition of atorvastatin was able to counteract this phenomenon by down-regulating platelet NOX2 activation and isoprostane formation simultaneously reducing platelet activation (42). Moreover, extra-platelet nucleate sources of TX generation driven by low-grade inflammation or aspirin insensitive eicosanoid biosynthesis induced by enhanced oxidative stress may act as aspirin-insensitive agonists of the platelet TX receptor and thus act as further determinants of hypo-responsiveness to aspirin (Figure 1).

In contrast, compelling evidence suggests that hyperglycaemia does not influence the effect of aspirin. Indeed, 100 mg of aspirin have been shown to adequately suppress platelet activation in patients with T2DM, irrespective of their glycaemic control and comparable to the effect in healthy subjects (43). Extensive glycation of platelet and coagulation factor proteins has been shown to interfere with their acetylation (44), although a specific effect of glycation on the acetylation of the critical residues in the catalytic pocket of COX-1 has never been reported. In a population of patients with coronary artery disease, metabolic syndrome without DM was just as likely to have an inadequate effect of aspirin on PGHS-1 as metabolic syndrome with DM (45). Thus, metabolic features other than blood sugar emerge as potential determinants of inadequate pharmacological effect of aspirin.

On a different note, tight glycaemic control has been shown to favourably impact cardiovascular morbidity, and thus the absolute risk of events, especially when achieved in patients with newly diagnosed diabetes (46), as a consequence of the “legacy effect”. Furthermore, blood sugar control, as well as control of other risk factors by disease-modifying drugs, has been shown to also reduce atherosclerotic plaque growth and disruption, that per se adds another thrombotic risk by thrombin generation (47). Thus, the

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**Figure 1:** Diabetic subjects may have impaired response to aspirin through several mechanisms. Pharmacodynamics variation may be due to accelerated platelet turnover, leading to newly released platelets with non-acetylated COX-1 during the 24-h dosing interval, despite the once-daily low-dose aspirin regimen. This may be normalised by a twice-daily regimen. Furthermore, low-grade inflammatory state and oxidative stress may contribute to generation of aspirin-insensitive agonists of thromboxane receptor (i.e. COX-2-generated TXA₂ and systemic and intraplatelet F₂-isoprostanes), resulting in residual platelet activation. Statins have been shown to blunt, at least in part, these latter mechanisms.
benefit of aspirin, in well-controlled diabetic patients with multiple drugs on board, might be weakened, in the absence of a true failure of aspirin to inhibit its drug target.

**Accelerated platelet turnover**

The most convincing and proven mechanism of less-than-expected response to aspirin appears to be increased platelet turnover. In fact, non-acetylated COX-1 and COX-2 in newly formed platelets may provide a biologically plausible explanation for aspirin-insensitive TXA₂ biosynthesis.

Recently, we described a similar pattern of inter-individual variability in the rate of turnover, and recovery, of platelet COX-1 activity among patients with or without diabetes during a 24-hour (h) interval in aspirin dosing (48), with approximately one-third of patients in each group showing a substantially faster rate of recovery of COX-1 activity. This was unrelated to glycaemic control, but was likely to be due to abnormal megakaryopoiesis, obesity, or both, since on multiple regression analysis, higher mean platelet volume (MPV) and body mass index (BMI) in the DM group and higher body weight in the group without DM were the only independent predictors of accelerated COX-1 recovery.

Due to the 20-minute half-life of aspirin, in the presence of accelerated megakaryopoiesis and enhanced platelet turnover, even 10-fold of basal rate, leading to accelerated renewal of the drug target, newly generated platelets entering the circulation may not be sufficiently exposed to aspirin if given once daily. Thus, a proportion of circulating platelets with uninhibited COX-1 activity may be responsible for accelerated recovery of TX generation in the 12–24 h dosing interval. This phenomenon can be detected in the peripheral blood by measuring time-dependent changes in serum TXB₂ during the 12–24 h aspirin dosing interval after a witnessed administration. Recently, our and several other groups have suggested that inadequate TX inhibition can be easily measured and corrected by a twice-daily low-dose aspirin regimen (48,49).

In our diabetic population (48), the shorter duration of COX-1 suppression in about one-third of the studied population, its independent association with MPV, and with young, reticulated platelets, mirroring platelet turnover, and reversal by a twice-daily aspirin regimen, are consistent with the hypothesis of accelerated renewal of the drug target during the dosing interval in T2DM. These findings may explain, independently of non-compliance, a variable dilution of the maximal theoretical effect of aspirin as an antithrombotic agent, depending on the prevalence of the factors influencing aspirin pharmacokinetics (e.g. obesity) or pharmacodynamics (as in diabetes) (Figure 1). This may have important clinical implications since the pharmacokinetics issue will prompt evaluation of the widely employed enteric coated aspirin formulations, which may yield reduced drug bioavailability (37), whereas the pharmacodynamics issue will stimulate testing personalised dosing regimens to overcome inter-individual variability.

**Discussion**

For people without pre-existing vascular disease, including diabetic patients, the cardiovascular benefits of adding long-term aspirin to other primary prevention strategies (e.g. statins and antihypertensive drugs) are of similar magnitude as the hazards (3). The size of the absolute benefit of aspirin could be halved by the cardiovascular risk reduction associated with statin therapy (3), thus abolishing the difference between the number of vascular events avoided and major bleeds caused by aspirin. However, the same halving of the absolute excess of bleeding complications could be obtained from the use of cytoprotective strategies (such as proton pump inhibitors or H. pylori eradication) (50).

Despite suggestive evidence for a potential role of aspirin in cancer prevention, clinical guidelines for primary prevention currently consider only the cardiovascular benefits and whether these outweigh the potential harm from aspirin-induced bleeding. Thus, no attempt to integrate cancer prevention with the cardiovascular benefits of treatment has been done.

The routine use of aspirin in apparently healthy individuals, including diabetic persons, is suggested above a moderate level of coronary risk, unless additional long-term benefits of aspirin therapy will be established. Two ongoing primary prevention trials in diabetes mellitus (ASCEND and ACCEPT-D) (27, 28), if meeting their recruitment goal, maintaining high adherence and follow-up, and accruing a sufficient number of clinical endpoints, may help assess the benefit/risk profile of low-dose aspirin in preventing multiple outcomes. In the meantime, a personalised choice should be made after considering also patient’s preferences and values together with clinical judgment.

However, as suggested by aspirin sceptics (51), what we need is a definitive, modern trial of aspirin for primary prevention, maybe in people already taking statins. Will the ASPREE study (52), also including patients with diabetes, which has a unique composite endpoint to better capture the overall risk and benefit of aspirin, be this definitive trial?

Despite the validation of multiple diabetes-specific and general population-based cardiovascular risk assessment models, estimation of an individual’s cardiovascular risk remains approximate, and whether new biomarkers of risk will improve risk assessment is still an open question. In perspective, the indication to low-dose aspirin prescription in primary prevention should be slowly fine-tuned from the mere calculation of 10-year cardiovascular risk, to a precise characterisation, or phenotypisation, of individuals who would attain inadequate protection from aspirin, and for whom different strategies should be challenged. In this regard, the predictive value of higher BMI, MPV, platelet or systemic isoprostane concentrations, etc, as biomarkers of the risk to receive less-than-adequate antithrombotic effect should be prospectively tested before replacing current approaches. However, whilst this approach is theoretically attractive, conducting randomised trials based on biomarkers is extremely challenging. Moreover, demonstrating that a novel biomarker is predictive of cardiovascular disease is, by itself, insufficient proof that it adds incremental value to existing risk estimation models. In this regard, evaluation of the above
mentioned candidate biomarkers for their Net Reclassification Improvement index, and their addition to conventional risk estimation, may be useful in correctly reclassifying individuals at intermediate risk as above or below a chosen intervention threshold (53).

In parallel, novel antithrombotic strategies, specifically targeting the pathophysiology underlying less-than-expected response to aspirin, should be challenged. In this regard, an association between statins and aspirin as compared to aspirin alone would be of particular interest, because statins could counteract the up-regulation of platelet isoprostanes elicited by aspirin in patients with T2DM. The ACCEPT-D trial is currently ongoing, testing the efficacy of aspirin 100 mg daily top simvastatin 20 mg daily, vs no aspirin therapy, in diabetic patients without clinically manifest vascular disease with an indication for statin treatment (28).

Finally, a 75 mg twice-daily regimen, shown to overcome incomplete platelet COX-1 suppression in the 24-h interval in diabetic as well as in non-diabetic subjects at cardiovascular risk (34), may be worth testing in the setting of a randomised clinical trial, in order to definitely assess whether the normalisation of the biochemical phenotype, in terms of kinetics of COX-1 recovery, attained with a more frequent aspirin dosing regimen, will translate into a clinical benefit in terms of hard vascular endpoints, without additional safety concerns (bleeding event rates are relatively flat to 150 mg and rise thereafter (26)).

Conclusions

While waiting till the time is ripe for changing the design of clinical trials based on the pathophysiology, we should in the next months give greater attention to the importance of the data from the ongoing ASCEND (27) trial of diabetic patients and ARRIVE (54) trial of moderate to high-risk primary prevention subjects, before making firm recommendations.

Acknowledgments

The expert editorial assistance of Dr Paola Simeone is gratefully acknowledged. This study was partially funded by a grant from CARIPLO, Scientific Research in Biomedicine 2011, to GD and FS.

Conflicts of interest

None declared.

This Viewpoint Article reflects the view of its author(s) and is not representative of the view of the Editorial Board or the Publishers.

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