Letters to the Editor

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Relationship Between Stroke Relative Risk and Change in Systolic Blood Pressure: The Misuse of Meta-Regression

To the Editor:

In their recent review on the relationship between change in blood pressure and risk of stroke, Lawes et al. reported that a 31% relative risk reduction (RRR) may be expected from a 10 mm Hg decrease in systolic blood pressure (SBP). This point estimate was derived from a meta-regression based on 7 meta-analyses of 47 controlled clinical trials, regressing the pooled RRR against the average difference in SBP change between treatment groups. Out of the 7 meta-analyses used in the meta-regression, 3 compared an active treatment versus placebo, 1 a more intensive versus less intensive treatment, and 3 compared 2 different classes of antihypertensive treatments. The authors emphasized that for a 10 mm Hg decrease in SBP, the 31% RRR estimated from clinical trial results is (nicely) consistent with the 25% to 36% RRR observed in population-based epidemiological cohorts. The conclusion is that the effect obtained by pharmacological treatments to decrease SBP may directly translate into a decrease in stroke risk at a population level.

I would be cautious about these results.

First, the authors should have given a 95% CI around their 31% point estimate, which I calculated to be (12.2%–49.8%); ie, covering a quite wide spectrum of values.

Second, and more problematic, is the choice of the control groups in their meta-analysis. For example, in 1 of the 7 meta-analyses, β-blockers and/or diuretics were compared with calcium antagonists, yielding a RR of 1.08 (95% CI, 0.99 to 1.16) for an average decrease in SBP of 1 mm Hg. As well, the authors could arbitrarily have chosen to compare calcium antagonists to β-blockers/diuretics, yielding a RR of 0.92 (ie, 1/1.08) for an average increase in SBP of 1 mm Hg. Using the latter comparison in the meta-regression instead of the former provides an estimated relationship between RRR and SBP difference of 22% (95% CI, 14% to 30%), quite different from the published 31%.

Third, if instead of using pooled RR and average SBP effects from the 7 meta-analyses they had used the raw results observed in the 47 trials to perform the meta-regression, the estimated slope would have been equal to 22% (95% CI, 14% to 30%). If blocker/diuretic and calcium antagonist groups were reversed as above, the slope would have further decreased to 17% (95% CI, 7% to 21%).

Meta-regression is subject to several potential pitfalls. Appropriate modeling methods should be used, with cautious interpretation of the results. A fundamental difficulty with meta-regression may be the choice of the reference group such that all treatment comparisons have common meaningful effects across trials (eg, active treatment versus placebo, high dose treatment versus low dose treatment). As exemplified here, situations exist where no obvious reference group can be identified for some comparisons, leading to different results depending on which reference group was arbitrarily considered.

In short, the 31% reduction in stroke risk for 10 mm Hg SBP reduction published by Lawes et al. is subject to important variations depending on the analysis performed. It should not be taken for truth in future medical papers.

Response:

We thank Drs Messerli, Fonier, and Boutitie for their comments. Drs Messerli and Fonier suggest that β-blockers are less effective than other agents, especially for stroke prevention. The benefits of β-blockers are difficult to assess precisely, since there are few direct randomized comparisons with other agents and most trials of β-blockers also included other blood pressure lowering interventions (most commonly, diuretics). However, inference is not aided by focus on underpowered individual studies; eg, Drs Messerli and Fonier quote the TEST and Dutch TIA trials, but the blood pressure reductions achieved in these trials were only a few mm Hg and so, unsurprisingly, their results were equivocal. The evidence from direct randomized comparisons does not indicate a clear difference for β-blockers compared with diuretic-based therapy and this is consistent with the dose-response we observed. Furthermore, the clear evidence of benefit from β-blockers among patients with coronary disease and heart failure makes it extremely unlikely that there would be “complete inefficacy” in patients whose predominant diagnosis is hypertension. Hence we maintain that the totality of the evidence shows no detectable difference between the main drug classes mm Hg for mm Hg in their reductions in stroke and coronary heart disease risk. Since all agents lower blood pressure by about the same modest amount, and their effects are additive, the key issue seems to be which combinations of 2 or more drugs should be provided and how long-term adherence can be maximized.

We are grateful to Dr Boutitie for her thorough review of our article and calculating confidence intervals for meta-regression slope estimates. We agree that any meta-regression is subject to a number of limitations, and there are instances in which there is no obvious reference group and some arbitrary choices are required. However, we do feel that, ideally, overviews should be based on the individual participant results from trials rather than collated trial results. The other meta-regression estimates presented by Dr Boutitie are all consistent with the epidemiological associations (one quarter to one third lower stroke risk per 10 mm Hg), given an appropriate degree of uncertainty about the precision provided by this method.

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Re: Lawes et al: Blood Pressure and Stroke

To the Editor:

We would like to commend Dr Lawes and collaborators\(^1\) on their thorough overview of antihypertensive therapy and stroke. However, we take issue with their conclusion that “initiating and maintaining BP reduction for stroke prevention is a more important issue than choice of initial agent.” This may well be true for most antihypertensive drugs, but not for the \(-\beta\)-blockers.

There are no conclusive data showing that \(-\beta\)-blocker-based therapy reduces the risk of strokes or heart attacks in uncomplicated hypertension.\(^2\) To the contrary, in the double-blind prospective randomized Dutch TIA Trial, atenolol, despite lowering blood pressure, did not reduce strokes better than placebo.\(^3\) A similar lack of efficacy of atenolol was demonstrated in the double-blind Tenormin After Stroke and TIA study in hypertensive patients with established cerebrovascular disease.\(^4\) In the Medical Research Council study, neither heart attacks nor strokes were significantly reduced with atenolol when compared with placebo in contrast to the reduction seen with a thiazide diuretic.\(^5\) Thus, 3 independent randomized trials attest to the inefficacy of \(-\beta\)-blocker-based therapy in reducing cerebrovascular events. In both the Swedish Trial in Old Patients with Hypertension\(^6\) and the Coope study,\(^7\) which are often quoted to support efficacy of \(-\beta\)-blockers, more than two thirds of patients concomitantly received diuretics, and outcome results for this combination obfuscates the complete inefficacy of the \(-\beta\)-blocker.

Unfortunately, Dr Lawes et al\(^8\) also lump \(-\beta\)-blockers and diuretics into the same category. Because diuretics-based therapy is one of the most powerful ways to reduce the risk of strokes,\(^8\) this combination obfuscates the complete inefficacy of the \(-\beta\)-blocker.\(^8\) Not surprisingly, in the LIFE study an angiotensin receptor blocker was much more efficacious than a \(-\beta\)-blocker in reducing cerebrovascular events.\(^9\) Clearly, with regard to stroke reduction, not all antihypertensive drugs are created equal.\(^10\)

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“Lacunarization” of Stroke Prevention Studies

To the Editor:

Recent stroke prevention studies that have compared differing antithrombotic regimens have been somewhat disappointing in that the more intense antithrombotic regimen has failed to demonstrate superiority over the more conservative regimen. Although this may reflect the fact that established therapy is difficult to improve on,\(^1\) I am concerned that the stroke subtype composition in these trials may be distorting the outcome and that they are not reflective of the larger community of patients with ischemic stroke.

As examples, in the Warfarin Aspirin Recurrent Stroke Study, the lacunar infarct patients represented 56.1% of the study cohort.\(^2\) In the African-American Antiplatelet Stroke Prevention Study, the small vessel infarct subtype accounted for 67.5% of patients.\(^3\) Finally, in the recently reported Management of Atherothrombosis With Clopidogrel in High-Risk Patients Study, 52.5% of patients had lacunar infaracts as the qualifying subtype.\(^4\)

Thus, to some extent, each of these studies could be viewed as a referendum on lacunar infarction treatment. In a study that excluded cardioembolic strokes, one would expect that ~40% of patients would have cryptogenic infarcts, and ~30% should have large vessel atherosclerotic and lacunar infarcts. The fact that recent studies are enrolling >50% of the study population as lacunar infarction patients does not seem representative of the larger spectrum of ischemic stroke patients. It also impairs subgroup comparison and hypothesis generation for future studies of large vessel atherosclerotic and cryptogenic infarction.

Clinical trialists who design future studies of “noncardioembolic stroke” should consider limiting lacunar infarct enrollment to ~50% of the study cohort and should try to avoid making the entry criteria overly restrictive so that only patients with minimal disability (who tend to be those with lacunar stroke) are allowed in the trial.

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The Unifying Role of Matrix Metalloproteinases in Atheroma and Vascular Stroke

To the Editor:

Two recent articles published in Stroke, 1 by Morgan et al3 and the other by Alvarez-Sabin et al2 highlight the role of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) in the pathogenesis of vascular disease. Cerebrovascular disease whether thrombotic, embolic or hemorrhagic is associated with abnormal vascular structure. Morgan et al show higher levels of collagenase transcripts in plaques in keeping with the hypothesis that these are physically unstable and prone to rupture. Plaque rupture in the cerebral circulation can be associated with in situ thrombosis and ischemic stroke or alternatively vascular rupture producing hemorrhagic stroke. Equally, in the carotid circulation a sub-acute plaque rupture may initiate mural thrombus and subsequent distal embolism resulting in embolic stroke associated with carotid atherosclerosis.

Given such a linkage, the findings by Alvarez-Sabin et al of higher levels of circulating MMPs and TIMPs in patients who experience hemorrhagic stroke is understandable. The strong associations with circulating markers of extracellular matrix turnover and hemorrhagic events in the studies of Alvarez-Sabin et al suggest that the MMP/TIMP system has a significant role in mediating vascular rupture. The association between perihematomal edema with higher levels of MMP-9, and lower levels of TIMP-1, strengthens the hypothesis that an interaction between enzyme and inhibitor is very important. Their data are consistent with an earlier study showing that circulating concentrations of MMP-9 are raised after spontaneous intracerebral hemorrhage.1

There are obvious connections between vascular pathologies in the coronary and cerebral circulations, sharing similar population risk factors. Although the arterial process is similar, cerebral and coronary arteries are exposed to different pressures, i.e., vascular wall stress and control factors. Notwithstanding these important differences, similar changes in circulating MMPs and TIMPs are in coronary arterial plaque.4 Extending the general role of MMP/TIMP in occlusive vascular events, recent work from our group on patients with diabetes and hypertension has suggested abnormal circulating levels of MMPs and TIMPs in hypertension1 and diabetes.5 We have found that MMP-9 may have prognostic value in predicting vascular events in hypertension and that there may be a possible link between cardiac stiffness and TIMP-1,7 as well as an increase in circulating neutrophil MMP-9 levels in stable coronary artery disease.6

In summary, the data of both Morgan et al and Alvarez-Sabin et al support a more general linking hypothesis that changes in MMPs and TIMPs are common to many different expressions of vascular disease. Although these processes remain distinct, they are linked at the basic level of vascular structural change. We would suggest that this process is, in large part, mediated by change in MMPs and TIMPs activities. It may be that in cerebrovascular states, as we have found in cardiovascular disease, that circulating levels may be a valid noninvasive assessment of vascular extracellular matrix turnover and propensity to vascular occlusion (whether ischemic, hemorrhagic or embolic). It is likely that changes in plaque turnover, suggesting instability, may provide a better functional assessment than imaging assessments of atheroma severity (angiographic or ultrasonic) and provide more accurate prognostic information to guide complex interventions such as carotid stenting or aneurysm surgery.

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White Matter Hyperintensities: Pearls and Pitfalls in Interpretation of MRI Abnormalities

To the Editor:

Atwood et al acknowledge that the pathophysiology of white matter hyperintensities (WMH) is uncertain and underscore the possibility of ischemic etiology, especially in the elderly.1 These authors regard WMH as an excellent marker of brain aging and emphasize their heritability in patients with negative correlation with cerebrovascular brain injury. WMH are neither age-specific nor generally heritable, having been found in both sexes in hypertensive encephalopathy, puerperal eclampsia, migraine, and therapy with cyclosporin, interferon-α, and tacrolimus.2-3 Kruit and coworkers found WMH in MRI only in women migraine patients2 which finding likely reflects an investigational artifact. Atwood et al did not exclude hypertensive and migraine patients from their analysis, which prominently confounds their interpretation of WMH as indicative of brain aging.

An important pathophysiologic clue to the nature of WMH is offered by the characteristic difference in the distribution of infarcts and deep WMH in migraine patients. Predominantly posterior circulation territory (PCT) migrainous infarcts in contrast to anterior circulation infarcts in embolic or atherosclerotic thrombotic strokes in general are likely related to rheological factors. Anatomical vulnerability of the posterior cerebral artery renders it particularly susceptible to vasospastic influences in migraine patients.4 The rare occurrence of neuroanatomically
nonlateralizing—in relation to headache or aura—PCT infarcts in younger migraineurs might represent an uncommon complication of an adaptive vasospasm that rarely reduces perfusion critically in a particularly labile region. A

Diffuse, nonlateralizing distribution of deep WMH unaffected by triptan use indicates that WMH do not reflect the outcome of vasospastic ischemia. Also, local changes during migraine attacks, eg, excessive neuronal activation or excitation should logically manifest lateralizing WMH. Deep WMH, in contrast to infarcts, likely resolve totally along with resolution of symptoms and signs after treatment of hypertension or withdrawal (or reduction of dose) of immunosuppressive agents. Vasogenic cerebral edema probably underlies WMH in hypertensive encephalopathy; breakdown of the blood–brain barrier has been shown in man and in rat models. Attack-related, inconsistently-lateralized, and prolonged (>48 hours) hyperperfusion prevails in the cerebral cortex, thalamus and basal ganglia in migraine. In direct contrast to infarcts, WMH probably result from intense but self-limited cerebral hyperperfusion. I propose that WMH are markers of transient breakdown of the blood–brain barrier rather than aging.

The heritability of WMH volumes is an intriguing feature. The decline in heritability estimates after age 60 indicates a nongenetic nature of this observation. Another indicator of the nongenetic nature of WMH is the absence of correlation with aging in women despite higher heritability. Migraine is more prevalent in females than in males, from approximately age 14. Breakdown of the aging-marker hypothesis for WMH in women may relate to heritability of hypertension or migraine or both. In the absence of any link to cerebrovascular disease, the menopause probably has no independent bearing on WMH. Spontaneous resolution likely underlies significantly smaller WMH volumes at younger age, especially in women, in which cohort the highest prevalence of migraine can be expected. These authors also hope to establish a genetic link between WMH and silent brain infarctions. Unless the resolution or otherwise of WMH is established prospectively, it is premature to link this MRI finding with cerebrovascular ischemic disease. Cross-sectional studies of WMH cannot establish vascular-related genetic influences, as has been suggested. Assumption of the genetic model for WMH is probably incorrect.

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Several studies show that magnesium does cross the blood–brain barrier, in both animals and in humans. Brain magnesium concentrations are regulated by active blood–brain barrier transport. Cerebrospinal fluid magnesium concentration increases by 20% to 25% in response to doubling of the serum concentration, and peaks around 4 hours after parental administration. While this overall increase in cerebrospinal fluid magnesium concentration is modest, magnesium concentration is selectively substantially increased in regions of pathology, including focal ischemia and seizures.

It is also well known that the mild negative inotropic effect of magnesium sulfate is offset by its lowering of peripheral vascular resistance, resulting in no clinically substantial impairment in cardiac pump function. Several physiological studies suggest that magnesium increases cardiac output. Even in patients experiencing active myocardial ischemia, magnesium sulfate showed only a small increase in the incidence of cardiogenic shock or congestive heart failure in the large ISIS–4 trial, and no adverse effect on cardiac pump function was reported in the more recent MAGIC clinical trial. Most saliently, among stroke patients in the phase 3 IMAGES trial, there was no excess of cardiac events related to administration of magnesium sulfate.

In addition, magnesium sulfate is a potent cerebral vasodilator, in part due to calcium channel antagonism at vascular smooth muscle cells and possibly effects on myosin-binding proteins that regulate contraction. Consequently, magnesium sulfate typically increases, rather than decreases, cerebral perfusion. Magnesium sulfate has been demonstrated to reduce infarct volume in multiple animal models of stroke, has numerous identified beneficial neuroprotective and vascular effects, is already known to be efficacious in treating in humans a condition characterized by altered cerebral blood flow (eclampsia), and has shown a potential signal of efficacy when administered early after stroke onset (within 3 hour subgroup) in a randomized clinical trial. Further trials of magnesium sulfate in early time epochs in acute stroke are well-supported by preclinical and clinical neuropharmacology.

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**Response:**

We thank Dr. Gupta for his interest in our study, but we strongly disagree with his assessment of the pertinent literature. In fact, the basic neuropharmacology of magnesium sulfate provides substantial support for clinical stroke trials in humans.
There Is No Evidence That the Benefit of Clopidogrel Over Aspirin Is Amplified in Patients With a History of Ischemic Events

To the Editor:

The article by Ringleb et al.\(^1\) does not prove that the benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. The article showed that among a subgroup of patients with preexisting atherosclerotic disease, taken from the CAPRIE trial,\(^2\) the relative risk reduction for the outcome of ischemic stroke, myocardial infarction or vascular death for clopidogrel over aspirin was 14.9% (95% CI, 0.3% to 27.3%). This was then compared with the results from the entire CAPRIE population, where the relative risk reduction was 8.7% (95% CI, 0.3% to 16.5%). The CIs for these 2 relative risk reductions overlap greatly, so (ignoring issues around the subgroup not being independent of the whole population) all one can say is that clopidogrel performed somewhat better than aspirin in the whole trial population, and clopidogrel also performed better than aspirin in the subgroup. The apparently increased treatment effect in the high-risk patients could easily have been a chance fluctuation.

To prove that the effect of clopidogrel is amplified in high-risk patients, one would need to test whether the treatment effect is different in high-risk patients to low-risk patients, using a formal test for interaction.\(^3\) The appropriate data for this calculation were not presented in the article, but from a rough calculation, we think it is unlikely that such a test would be statistically significant.

In addition to the problems with the statistical analysis, ‘high-risk’ has been defined by simply using a history of atherosclerotic disease. This is overly simplistic, and a more appropriate approach would be to use a prognostic model to divide patients into high-risk and low-risk groups.

It is worrying that an article with such a biased conclusion has been published in the name of the CAPRIE investigators. The authors were, we believe, from contributing clinical centers to the CAPRIE trial, but this article was not approved by the steering committee, as far as we know by the trial statistician.

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Are Neurologists More Likely to Prescribe Antithrombotic Therapy After Stroke?

To the Editor:

Volpato et al.\(^1\) in their recent work have highlighted the lack of antithrombotic treatment prescription at discharge from hospitals in a large proportion of patients after an ischemic brain attack. Although the rate of prescription was increased in the late 90s, 30% of patients did not receive antithrombotic treatment for secondary prevention. In the Neurology department of our hospital, there is a strong interest in stroke, so a stroke outpatient clinic was set up and has been running since early 2000. We, therefore, looked at our stroke register to find out the attitude of neurologists compared with that of the physicians in prescribing antithrombotic treatment after stroke.

During an 18-month period commencing in 2000, 278 patients (mean age 68.4±12.5, female 42%) with an acute ischemic stroke were discharged from Neurology and General Medicine wards of the University Hospital of Patras, Greece. The catchment area of our hospital is the city of Patras, which is the third largest city in Greece, and the smaller towns and villages of northwest Peloponnesus. All patients were invited at discharge to attend the stroke outpatient clinic at regular intervals (1, 3, 6 and 12 months from onset).

Antithrombotic treatment was prescribed in 223 (80%) of the 278 patients (13% aspirin alone, 75% ticlopidine, clopidogrel, or slow release dipyridamole with aspirin, and 12% oral anticoagulants). Of the 198 patients (mean age 63.8±11.3), who were discharged from the Neurology wards, 16 (8%) were not taking any antithrombotic treatment, compared with 39 (49%) of the 80 patients (mean age 79.7±7.2) discharged from the General Medicine wards (P<0.0001). Aspirin alone was prescribed in 5% and 50% of the patients on antithrombotic treatment in the Neurology and General Medicine wards respectively. Logistic regression analysis showed that among age, sex, residence (urban versus rural), discharge ward, vascular risk factors and cognitive impairment (Mini Mental State Examination score at discharge), only discharge ward was independently associated with not prescribing antithrombotic treatment (OR, 13.0; 95% CI, 5.4 to 31.2).

During the first year post-stroke, 197 patients attended the stroke clinic (81% of the first year survivors). Of these, 173 patients, who were discharged on antithrombotic therapy, showed excellent compliance with treatment throughout the first year of follow up. Of the 24 patients who were not on any antithrombotic treatment at discharge, 15 (63%) commenced...
treatment, whereas in the remaining antithrombotic treatment was contraindicated.

Our data show that a larger proportion of patients are prescribed antithrombotic treatment after stroke compared with that reported by Volpato et al. However, neurologists prescribed antithrombotic treatment at discharge significantly more often than internists, and this is independent of other confounding factors. Whether this is because of the special interest our neurologists have in stroke, to their greater exposure to the results of the multicenter randomized control trials and overviews, or to a targeted promotion of the newer antipatelet drugs, is not clear. The stroke outpatient clinic at the University Hospital of Patras helps to maximize the proportion of patients on preventive treatments, and possibly also helps to maintain the compliance with treatments, although, it is not possible with our data to tell whether the patients who did not attend the clinic complied with therapy. We are currently examining the prescription and compliance of preventive treatments for other modifiable stroke risk factors.

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Response:
We appreciate the interest of Drs Ellul, Talelli, and Papapetropoulos in our article on antithrombotic prescription in older Italian patients with ischemic brain events.\(^1\) We found a substantial rate of patients (~40%) discharged from internal medicine and geriatrics departments without antithrombotic therapy prescription. We also found that presence of physical and cognitive impairment was the most important independent factor related to the likelihood of having the antithrombotic prescription.

In their work, Ellul and coauthors reported a higher prevalence rate of antithrombotic prescription (80%) in a sample of 278 patients discharged with an ischemic stroke from neurology and general medicine wards. They also pointed out that patients discharged from neurology departments were more likely to receive antithrombotic treatment as compared with patients from general medicine wards. This difference was independent of age, gender, vascular risk factors, and cognitive impairment. The authors therefore concluded that neurologists are more prone than general physicians to adhere to international guidelines for ischemic stroke secondary prevention.

This hypothesis is interesting and certainly plausible; however, other potential explanations should be considered. Although the authors did account for important confounders, including age and cognitive status, other major clinical characteristics, potentially related to both drug prescription pattern and patient setting allocation, were not included in the analysis. Indeed, in our clinical experience, the more complex patients, characterized by older age, higher comorbidity level, physical disability, and polypharmacotherapy, are more likely to be admitted to a geriatric or internal medicine ward. In these complex patients, systematic application of guidelines is often challenging and not always feasible. Therefore, the lower antithrombotic prescription rate recorded in the general medicine department may be, at least in part, the result of a careful clinical evaluation and not the consequence of lack of adherence to evidence-based medicine. In keeping with this interpretation, a recent article reported a different prescription rate of statins according to age and cardiovascular risk profile with the oldest patients with the highest risk profile having the lowest probability of statins prescription.\(^2\)

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White Matter Hyperintensities: Pearls and Pitfalls in Interpretation of MRI Abnormalities
Vinod Kumar Gupta

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In the October issue of *Stroke*, the Letter to the Editor entitled, “White Matter Hyperintensities: Pearls and Pitfalls in Interpretation of MRI Abnormalities” by Vinrod Kumar Gupta was mistakenly published with a response by Saver et al. The Saver et al response refers to a letter by Gupta entitled “Intravenous Magnesium for Neuroprotection in Acute Stroke: Clinical Hope Versus Basic Neuropharmacology.” The two letters and their appropriate responses appear in this issue (pp 2758–2759). The publisher regrets this error and apologizes for any confusion it may have caused.