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ABSTRACT & COMMENTARY

High Blood Pressure: How Low Should We Go? SPRINT and a New Meta-analysis

By Martin Lipsky, MD

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Dr. Lipsky reports no financial relationships relevant to this field of study.

SYNOPSIS: The SPRINT study, which explored the effect of targeting blood pressure treatment to a goal of < 120 mmHg, ended early because of significantly lower rates of fatal and nonfatal cardiovascular events and death from any cause. However, the incidence of acute kidney damage hypotension, syncope, and electrolyte abnormalities were higher in the treatment group. A recent meta-analysis also supports the benefit of targeting lower blood pressure levels.

SOURCES: The SPRINT research group: A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-2116.

Xie X, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: Updated systematic review and meta-analysis. *Lancet* 2015 Nov. pii: S0140-6736(15)00805-3. doi: 10.1016/S0140-6736(15)00805-3. [Epub ahead of print].

The Oct. 29, 2015, issue of *Internal Medicine Alert* discussed the Systolic Blood Pressure Intervention Trial (SPRINT), which ended early because of a significantly lower rate of cardiovascular events in the intensive-treatment group than in the standard-treatment group.[1] All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% confidence interval [CI], 0.60-0.90; $P = 0.003$). However, at that time the full study was not yet published. Concerns about the risk of adverse events from aggressive treatment suggested a need for caution before translating the SPRINT findings into clinical practice. Indeed, an article in *The New England Journal of Medicine* about SPRINT reported that the rates of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.[2] However, despite the risk of acute renal injury, the authors noted there was no evidence of substantial permanent kidney damage associated with the lower systolic treatment group, although the possibility of long-term damage could not be excluded.

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In another study to help guide hypertension treatment, Xie et al conducted a meta-analysis examining the benefit and safety of intensive blood pressure-lowering strategies.[3] The study systematically searched Medline, Embase, and the Cochrane Library for trials published between 1950 and 2015. The analysis identified 19 randomized, controlled trials representing 44,989 participants. The average blood pressure in the more intensive blood pressure-lowering treatment groups was 133/76 mmHg, compared with 140/81 mmHg in the less intensive treatment groups. Patients in the more intensive treatment groups experienced a risk reduction for major cardiovascular events (14%; 95% CI, 4-222), myocardial infarction (13%; CI, 0-24), stroke (22%; CI, 10-32), albuminuria (10%; CI, 3-16), and retinopathy progression. However, there were no clear benefits on heart failure, cardiovascular death, total mortality, or end-stage kidney disease among the aggressive treatment study arms. The reduction in major cardiovascular events was consistent across patient groups, and additional blood pressure lowering had a clear benefit, even in patients with systolic blood pressure < 140 mmHg. The absolute benefits were greatest in trials in which all enrolled patients had vascular disease, renal disease, or diabetes. Serious adverse events associated with blood pressure lowering were only reported in six of the trials and had an event rate of 1.2% per year in intensive blood pressure-lowering group participants, compared with 0.9% in the less intensive treatment group (relative risk [RR], 1.35; 95% CI, 0.93-1.97). Severe hypotension was more frequent in the more intensive treatment regimen (RR, 2.68; 95% CI, 1.21-5.89; $P = 0.015$), but the absolute excess was small.

■ COMMENTARY

Hypertension is one of the most common chronic conditions primary care providers treat. While there is clear evidence that treating high blood pressure improves outcomes, the optimal treatment target remains uncertain. The JNC 8 guidelines[4] cited the ACCORD study,[5] which failed to demonstrate added benefit from more intensive hypertensive treatment for individuals with type 2 diabetes, as evidence against more aggressive treatment in high-risk patients.

In contrast, investigators ended the SPRINT early because of the benefits observed in the aggressive treatment group. Since epidemiologic studies indicate that the risk of cardiovascular events increases, beginning at blood pressures > 115/75 mmHg,[6] the SPRINT results intuitively make sense. However, many clinicians who struggle with managing the side effects from aggressive treatment expressed concern about the risk of adverse effects associated with aggressive treatment, even before *The New England Journal of Medicine* published the trial data. To no great surprise, the published paper found an increased risk of adverse effects among aggressively treated patients.

For those who favor lower treatment targets, the Xie et al meta-analysis provides additional evidence to support more intensive blood pressure lowering, including high-risk patients whose systolic blood pressure is < 140 mmHg. In combination with SPRINT findings, these results may lead to changes in hypertension treatment guidelines. The SPRINT writing group recognized that its findings differ from the ACCORD trial and noted that the difference between the trials could be due to study design, treatment interactions, or chance.[2] In an editorial accompanying the Xie meta-analysis, Brunströma and Carlberg expressed that some uncertainty remains about whether diabetics or very elderly patients will benefit from lower treatment targets (< 140/90 mmHg).[7]

Moving forward, defining optimal blood pressure treatment targets will likely not be easy. Until new guidelines become available, it seems that if physicians can achieve lower blood pressures without causing significant side effects, the evidence supports this approach. Since side effects can be significant, physicians should not lose sight of the importance of including non-pharmacological approaches, such as weight loss and dietary sodium restrictions, when prescribing treatment. While these approaches alone are insufficient for most patients, they may be the difference between achieving lower blood pressure

targets with fewer medications, lower doses, and fewer side effects. In the meantime, stay tuned for the next set of guidelines. ■

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ABSTRACT & COMMENTARY

Association of Coffee Consumption with Total and Cause-specific Mortality

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: Regular consumption of both caffeinated and decaffeinated coffee were found to be inversely associated with risk of total mortality and mortality attributed to cardiovascular disease and neurologic diseases.

SOURCE: Ding M, et al. Association of coffee consumption with total and cause-specific mortality in three large prospective cohorts. *Circulation* 2016;132:2305-2315.

The associations between coffee consumption and increased risks of several disease outcomes have been well investigated. Coffee consumption in moderation has been inversely associated with increased risks for the development of type 2 diabetes mellitus, hepatic cancer, endometrial cancer, prostate cancer, skin carcinoma, neurologic diseases, and cardiovascular disease.[1-7] Multiple studies have reported an inverse association between moderate coffee consumption and risk of mortality and an inverse or null association between heavy coffee consumption and mortality risk.

Because of the inconclusive results of these multiple studies, Ding et al decided to determine the association of coffee consumption with total and cause-specific mortality in three large ongoing, independent cohort studies of men and women.

Researchers analyzed coffee consumption and total mortality in the Nurses' Health Study (NHS), consisting of 121,700 female participants; NHS II, consisting of 115,671 female participants; and the Health Professionals Follow-up Study (HPFS), consisting of 51,529 male subjects. The highest categories of consumption of total and caffeinated coffee were associated with a higher risk of all-cause mortality across the three cohorts. However, this finding was attenuated significantly after adjusting for smoking. In fact, in the entire population, coffee consumption was inversely associated with risk of mortality attributed to cardiovascular disease, nonlinearly associated with risk mortality associated with type 2 diabetes mellitus patients, and positively associated with risk of mortality attributed to lung cancer and respiratory diseases. The authors concluded that there existed a nonlinear association between coffee consumption and risk of mortality in the overall population, with moderate coffee consumption associated with lower mortality risk and high coffee consumption not associated with increased mortality risk. The authors noted that this association became linear and inverse after restricting it to the never-smokers group of patients, and therefore it was considered likely that the nonlinear association observed in the total population was attributed to the residual confounding by cigarette smoking.

■ COMMENTARY

It should be noted that this study analyzed the health and mortality results of coffee intake. The age-adjusted analysis revealed that the highest categories of consumption of total and decaffeinated coffee were associated with a higher risk of all-cause mortality across the three cohorts. However, the association attenuated significantly after further adjusting for cigarette smoking. Although coffee consumption was inversely associated with the risk of mortality attributed to cardiovascular disease, it was nonlinearly associated with risk mortality attributed to type 2

diabetes mellitus and positively associated with risk of mortality attributed to lung cancer and respiratory diseases. When coffee consumption was analyzed in never-smokers, it was no longer associated with risk of mortality attributed to lung cancer and respiratory disease, but was inversely associated with risk of mortality attributed to cardiovascular disease, neurologic disease, and suicide. Finally, it should be noted that the authors commented on the fact that they could not directly establish a cause-effect relationship between coffee and mortality because of the observational nature of the study design.

In conclusion, clinicians should be aware that regular consumption of both caffeinated and decaffeinated coffee was inversely associated with risk of total mortality and mortality attributed to cardiovascular disease and neurologic diseases. Patients can incorporate coffee into a healthy lifestyle without fear of coffee in and of itself causing harm. ■

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ABSTRACT & COMMENTARY

Should Postmenopausal Women Be Encouraged to Take Calcium?

By Jeffrey T. Jensen, MD, MPH

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SYNOPSIS: A systematic review of randomized, controlled trials of calcium supplementation found only small non-progressive increases in bone mineral density. This supports the clinical conclusion that supplementation alone is insufficient to prevent fracture risk.

SOURCE: Tai V, et al. Calcium intake and bone mineral density: Systematic review and meta-analysis. *BMJ* 2015;351;h4183. doi: 10.1136/bmj.h4183.

The authors conducted a systematic review of published randomized trials to evaluate the effects of increasing calcium intake on bone mineral density (BMD). Eligible studies recruited participants > 50 years of age and randomized subjects to receive increased dietary sources of calcium or calcium supplements (with or without vitamin D) or no additional calcium. Most of the studies enrolled only women. Studies could assess the outcome of BMD at the lumbar spine, total hip, femoral neck, total body, or forearm. They identified 15 trials that evaluated dietary sources of calcium (n = 1533 subjects). Of these, 10 used milk or milk powder, two used dairy products, and three used hydroxyapatite preparations. Calcium supplements (typically 1000 mg/day) were evaluated in 51 trials (n = 12,257); 36 studied calcium monotherapy, 13 co-administered calcium and vitamin D, and two compared both approaches. Most of the studies evaluated calcium without vitamin D in women < 70 years of age and had a duration of at least 2 years.

Overall, calcium supplements increased BMD at all five skeletal sites at 1 year (0.7-1.4%) and 2 years (0.8-1.5%). In studies that followed subjects longer, the size of the increase in BMD was similar to the increase at 1 year. Augmenting calcium intake from dietary sources also increased BMD at the total hip and total body at 1 year (0.6-1.0%) as well as the lumbar spine/femoral neck at 2 years (0.7-1.8%), but there was no effect on BMD at the forearm at either time point. Similar increases in BMD were observed in the trials comparing calcium to co-administered calcium and vitamin D, in trials with calcium doses

of ≥ 1000 mg/day vs < 1000 mg/day, and in trials where the baseline dietary calcium intake was < 800 mg/day vs ≥ 800 mg/day. The authors concluded that increasing calcium intake from either dietary sources or supplements results in only small and non-progressive increases in BMD that are unlikely to lead to a clinically significant reduction in risk of fracture.

■ COMMENTARY

In early menopause, rapid bone loss occurs due to the absence of estrogen-regulated modulation of bone remodeling. In addition to direct effects on bone, estrogen also has important effects on vitamin D metabolism and the intestinal absorption and renal excretion of calcium.[1] Since serum calcium levels actually decline in postmenopausal women in the setting of this massive turnover of calcium,[2] calcium supplementation is a routine recommendation. However, given the poor absorption and rapid excretion of calcium, I have always questioned whether the net effect of ingestion of an oral calcium supplement on calcium balance is similar to the effect of dropping a 10-pound bag of salt in the bay on ocean salinity. Although this meta-analysis provides no new information, the authors do raise a valid question. Since the overall impact of calcium supplementation on BMD is small and non-progressive, can this actually improve health by reducing fracture risk?

Clinical trials measure BMD as a surrogate for fracture risk, as large numbers of subjects must be followed for many years to actually evaluate fracture as a clinical endpoint. The studies evaluated in this meta-analysis have insufficient numbers to address the risk of facture. We also know little about the effect of age and, in particular, whether early replacement could be more impactful. When I discussed this paper with Leon Speroff, he was also careful to point out that "while the increase from baseline was not progressive, we typically expect to see a progressive bone loss accumulating with age, so prevention of that loss may well be meaningful in terms of fracture protection, particularly with long-term exposure." The most important clinical point to stress is that calcium and calcium/vitamin D should not be recommended for fracture prevention, in keeping with standard practice. In contrast, we have level 1A evidence that postmenopausal estrogen replacement therapy does prevent hip and other fractures.[3,4] Although women using raloxifene had a reduction in spinal compression fractures, an important reduction in hip fracture was not observed.[5,6] A reduction of non-vertebral fracture has also been reported with bazedoxifene, but the absolute number of hip fractures was small and not different from placebo or raloxifene.[7] Bisphosphonates have been shown to reduce vertebral and non-vertebral fracture risk, but the data are less convincing8 for primary prevention of hip fracture. This leads me to conclude that women at risk for fracture without contraindications to estrogen therapy should be strongly counseled to consider this benefit.

So calcium might help, but it should not be relied upon to prevent fracture in high-risk women. In my opinion, this information should be part of the discussion of initiation of estrogen therapy in healthy menopausal women. ■

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PHARMACOLOGY UPDATE

Elbasvir and Grazoprevir Tablets (Zepatier)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved another oral interferon-free regimen for the treatment of chronic hepatitis C (HCV) genotypes 1 and 4. This fixed combination of two direct-acting antiviral agents contains an inhibitor of HCV NS5A, elbasvir (EBR) and an inhibitor of HCV NS3/4A protease, grazoprevir (GZR). EBR/GZR was granted breakthrough therapy designation and is marketed as Zepatier.

INDICATIONS

EBR/GZR is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infections in adults.[1]

DOSAGE

The recommended dose is one tablet once daily with or without food.[1] The duration of treatment is 12 weeks for those with genotype 1a (without NS5A polymorphism) or genotype 1b in patients who are treatment-naïve (TN) or peginterferon/ribavirin-experienced, and treatment-naïve genotype 4 infections. For genotype 1a and 1b patients who are peginterferon/RBV- and protease inhibitor-experienced (TE), treatment duration is 12 weeks with the addition of ribavirin. For genotype 1a positive for NS5A polymorphism, or peginterferon/RBV treatment-experienced genotype 4, treatment duration is 16 weeks with ribavirin. Dose is the same with or without cirrhosis or any degree of renal impairment. EBR/GZR is available as tablets, each containing elbasvir (50 mg) and grazoprevir (100 mg).

POTENTIAL ADVANTAGES

EBR/GZR provides another option for the treatment of chronic HCV genotypes 1 and 4. The drug may be used in patients with renal impairment, including those with end-stage renal disease on dialysis.[1] It also may be used in cirrhotic patients at the same dose as non-cirrhotic patients.

POTENTIAL DISADVANTAGES

EBR/GZR is less effective in HCV genotype 1a with baseline NS5A polymorphisms at amino acid positions 18, 30, 31, or 93.[1] The estimated prevalence is 12%.[2] EBR/GZR is contraindicated in patients with moderate or severe hepatic impairment. EBR is a substrate of OATP1B1/3, and both EBR/GZR are substrates of CYP3A4. Co-administration with an OATP1B1/3 inhibitor or strong inducers of CYP3A and efavirenz are contraindicated. There is higher systemic exposure of EBR and GZR in females and Asians. These populations experienced a higher rate of late ALT elevations in clinical trials.

COMMENTS

EBR/GZR is a combination of two direct-acting antiviral agents with different mechanisms of action and non-overlapping resistance profiles.[1] Its efficacy was shown in two placebo-controlled trials and four uncontrolled trials.[1] These included TN and TE subjects with genotypes 1 and 4, with and without cirrhosis or co-infected with HIV-1.[1] The efficacy endpoint is sustained viral response 12 weeks after cessation of treatment (SVR12). Overall, SVR12 was 95% with or without HIV-1 co-infection. SVR12 was slightly higher numerically in genotype 1b, 98% vs 92% and 96% vs 94%, respectively. The sustained viral responses for cirrhotic vs non-cirrhotics were 97% vs 94% and 100% vs 94%, respectively. In TE subjects who failed prior peginterferon with RBV, with or without cirrhosis, SVR12 was 94% as monotherapy (12 weeks) and 97% for combination with ribavirin (16 weeks). Rates were similar in both cirrhotic and non-cirrhotic subjects. The overall SVR12 was 94% for subjects with severe renal impairment. In TE subjects who failed peginterferon/RBV and protease inhibitor, overall SVR12 was 96%. In subjects with genotype 4, SVR12 ranged from 97-100%. Adverse events include fatigue, headaches, nausea, elevation of ALT, and serum bilirubin.[1]

CLINICAL IMPLICATIONS

EBR/GZR provides another option for the treatment of HCV genotypes 1 and 4. It provides single tablet, interferon/RBV-free regimen for treatment-naïve or peginterferon/RBV-experienced genotype 1a (without baseline NS5A polymorphism), genotype 1b and treatment-naïve genotype 4. It also offers a new treatment option for patients with chronic kidney disease and a shorter treatment duration (12-16 vs 24 weeks) for some TE patients with cirrhosis. The current American Association for the Study of Liver Diseases/Infectious Diseases Society of America guideline for interferon/RBV-free option is ledipasvir/sofosbuvir.[3] EBR/GZR offers a significant cost advantage: $18,200 for a 28-day supply compared to $31,500 for ledipasvir/sofosbuvir. ■

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Clinical Briefs

By Louis Kuritzky, MD

Can Vitamin D Deficiency Cause Hypertension?

SOURCE: Chen S, et al. *J Am Soc Hypertens* 2015;9:885-901.

Should we just cut to the chase and accept that vitamin D deficiency causes everything? That's the way it seems these days. Chen et al made a convincing case for at least a potential etiologic role of vitamin D in development of hypertension.

Premises for consideration of vitamin D in relationship to hypertension include the observation that persons with less opportunity for vitamin D metabolism as a result of living in higher latitudes, having skin of color, or living in a colder climate with less outdoor sun exposure manifest a higher prevalence of essential hypertension. As part of "proof of concept," one clinical trial enhanced vitamin D through ultraviolet B radiation in vitamin D-deficient patients, resulting in lower blood pressure.

While it should seem simple to test the vitamin D-hypertension relationship hypothesis, the results of 40 randomized trials addressing the issue have been mixed. The authors provided some explanation for this by noting that younger hypertensives (< 45 years of age) have more effective counterregulatory mechanisms for maintaining vascular tone than older patients, and, hence, vitamin D repletion in younger patients has less effect on blood pressure. Since most trials have incorporated populations of diverse age, younger patients may have diluted potential blood pressure effects of vitamin D repletion.

The authors noted that vitamin D deficiency tends to lead toward vasoconstriction, a common component of essential hypertension. Perhaps identification of particular populations that are strong responders (and elimination of non-responder groups from clinical trials) will define better a therapeutic role for the prevention or treatment of hypertension with vitamin D. ■

Why We Can't Allow Physical Exam Skills to Languish

SOURCE: Verghese A, et al. *Am J Med* 2015;128:1322-1324.

With more highly evolved and readily available technology at our fingertips, it is sometimes tempting to let the echocardiogram sort out the abnormal heart sounds we detected, or allow the pelvic ultrasound to inform whether the uterus is enlarged, or short-cut parts of the physical exam we anticipate to be unlikely sources of pertinent information. At the same time, there may not be large-scale clinician awareness that a textbook of *Evidence-based Physical Diagnosis* even exists. (McGee, S. *Evidence-based Physical Diagnosis*, 3rd Edition. Philadelphia: Elsevier Saunders Publishers; 2012.) Could over-reliance on technology lead to meaningful errors?

Verghese et al reported on 208 vignettes that were volitionally reported to them in response to a survey soliciting instances of oversights related to the physical exam. The most common consequence of an inadequate physical exam was missed/delayed diagnosis. However, unnecessary treatment, delay in treatment, unnecessary exposure to radiation or contrast, and complications related to treatment were also reported.

Commonly missed items included abdominal masses, pregnancy, neurologic findings, murmurs, adenopathy, breast masses, heart failure, and herpes zoster. The authors reported that most of the cases in which inadequate physical examination led to consequences were the result of simply not performing the appropriate physical exam (rather than, for example, misinterpretation of an appropriately performed exam).

The authors made a case for reminding clinicians that appropriate physical examination skills need to be taught and maintained. Inadequate performance of the physical exam, as documented here, can lead to important consequences. ■

Teasing Relationships: Uric Acid, Fructose, and Hypertension

SOURCE: Madero M, et al. *J Am Soc Hypertens* 2015;9:837-844.

Uric acid has been under scrutiny for decades since its identification as a cardiovascular risk factor in the Framingham Heart Study. Whether elevations in uric acid are causally related to cardiovascular disease continues to be hotly debated. Elevations of plasma and intracellular uric acid are associated with higher blood pressure. Similarly, fructose, especially high-fructose corn syrup, has been suspect for its contribution to metabolic syndrome. Since fructose leads to increased intracellular and serum uric acid, a plausible pathologic pathway is evident.

Madero et all performed a two-step, controlled trial among 72 obese prehypertensive patients to examine the sequential effect of restricted dietary fructose for 4 weeks, followed by the addition of allopurinol 300 mg/day for another 4 weeks, compared to a control group. All subjects were advised to restrict sodium.

There was a trend for greater blood pressure reduction in the low-fructose diet group that did not achieve statistical significance. A post-hoc analysis of the second step of the trial (adding allopurinol to the diet) produced a reduction in office systolic blood pressure compared to the control group, but not in systolic blood pressure as measured by ambulatory blood pressure monitoring, which is considered more accurate and a better predictor of adverse effects of blood pressure. The roles of fructose restriction and allopurinol need more clarification. ■

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CME QUESTIONS

1. Which of the following statements is true?

a. Aggressive blood pressure treatment improves heart failure outcomes.

b. The risk of cardiovascular events increases starting at blood pressure levels above 115/75.

c. The ACCORD trial failed to demonstrate added benefit from more intensive hypertensive treatment for individuals with type 2 diabetes.

d. JNC 8 recommends treatment targets of 120/80 mmHg for individuals with hypertension.

e. Both b and c

2. Regular consumption of regular or decaffeinated coffee was found to:

a. be associated with an increased risk of total mortality.

b. be inversely associated with risk of total mortality and mortality attributed to cardiovascular disease and neurologic disease.

c. have no effect on total mortality.

d. be associated with an increased risk of mortality attributed to cardiovascular disease and neurologic disease.

3. In a recent meta-analysis, calcium supplementation for postmenopausal women was associated with which of the following?

a. A reduction in non-vertebral and vertebral fractures

b. A reduction in non-vertebral fractures only

c. Annual increases in bone mineral density of 2%

d. A small increase in bone mineral density at 1 year that was non-progressive

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

We Need Your Help!

The editors of *Internal Medicine Alert* are planning topics for 2016 issues and would like your feedback on topics recently covered. Please help us by answering three questions at the following link: ***https://www.surveymonkey.com/r/IMASurvey2016***. Thank you for your help!