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ABSTRACT & COMMENTARY

Prior Metformin Use in Patients with Diabetes Hospitalized for COVID-19

By Austin Ulrich, PharmD, BCACP

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SYNOPSIS: Investigators found metformin use before COVID-19 hospitalization for patients with diabetes was associated with a lower risk of death.

SOURCE: Lalau JD, Al-Salameh A, Hadjadj S, et al. Metformin use is associated with a reduced risk of mortality in patients with diabetes hospitalised for COVID-19. *Diabetes Metab* 2020; Dec 10;101216. doi: 10.1016/j.diabet.2020.101216. [Online ahead of print].

Metformin is a first-line treatment for type 2 diabetes, one of the most common comorbidities linked to the severity of COVID-19. Historically, metformin has been studied as an agent with potential antimicrobial and immunosuppressive effects, demonstrating positive results against hepatitis B virus, tuberculosis, malaria, Legionella pneumonia, and Zika virus.[1] The action of metformin on mitochondrial ROS/Ca2+ release-activated Ca2+ channels and IL-6 cascade has been theorized to mitigate the proinflammatory and prothrombotic processes of COVID-19. Additionally, researchers have observed metformin-producing antifibrosis effects in the lungs.[2,3] Based on these mechanisms, it is possible metformin is useful in attenuating COVID-19 severity.

Lalau et al evaluated patients from the French nationwide CORONADO study to determine if prior metformin use was associated with improvement in prognosis for patients with diabetes who were hospitalized for COVID-19. The CORONADO study included patients hospitalized for COVID-19 from March 10, 2020, to April 10, 2020, at 68 French centers. Patients were included in the Lalau et al study if they had diabetes and had been admitted to a COVID-19 unit with confirmed COVID-19 diagnosis. The primary outcome was a composite of intubation or death within seven days of hospital admission. Secondary endpoints included the composite endpoint at 28 days of hospitalization and intubation, and death individually at seven and 28 days of hospitalization. Propensity scores were calculated

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and used during data analysis to minimize bias. The authors included 2,449 patients in the analysis (1,496 took metformin before hospitalization, 953 did not). Patients who took metformin were more likely to be younger and male, more likely to have a shorter duration of diabetes and higher hemoglobin A1c, and less likely to use insulin or experience complications from diabetes.

Patients who took metformin experienced a longer period between symptom onset and hospitalization (six days vs. four days) and reported more frequent symptoms related to COVID-19. There was no difference in patients who experienced the primary composite outcome for metformin non-users and metformin users (276 vs. 419, respectively; $P = 0.6134$). However, metformin users were less likely than non-users to experience the composite endpoint at hospital day 28 (488 vs. 369; $P = 0.0023$). Metformin users were less likely to die by hospital day 7 (122 vs. 153; $P < 0.0001$) and less likely to die by hospital day 28 (239 vs. 273; $P < 0.0001$). Interestingly, metformin users were more likely to be intubated by hospital day 7 (316 vs. 140; $P = 0.0001$) and by hospital day 28 (328 vs. 149; $P = 0.0001$).

The authors concluded prior use of metformin was associated with a lower rate of the composite endpoint (intubation and death) and a lower rate of death within 28 days of hospitalization for patients with diabetes.

■ COMMENTARY

This study adds to the current body of evidence on metformin and COVID-19 outcomes. The authors of other observational studies have reported lower hospital mortality from metformin,[4] but some did not find this association.[5-8] Many of these other studies did not include body mass index (BMI) as a covariate or the sample sizes were smaller. Lalau et al included BMI as well as other key variables in developing propensity scores and recruited more patients. Several questions remain about the effects of metformin on COVID-19, including optimal dose and duration of metformin to provide protective effects, whether metformin treatment should be administered in the hospital, and whether metformin effects on COVID-19 can be generalized to all patients regardless of diabetes diagnosis. Still, practitioners may benefit from an awareness of the apparent protective effects of prior metformin use against COVID-19-related death for hospitalized patients with diabetes, despite a possible increase in symptoms related to COVID-19. ■

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ABSTRACT & COMMENTARY

How to Record Reliable Blood Pressure Measurements

By Michael H. Crawford, MD

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SYNOPSIS: A small, community-based study to detect hypertension revealed one week of twice-daily home blood pressure (BP) measurements are more reliable and more accurately predict increased left ventricular mass than clinic or 24-hour ambulatory BP monitoring.

SOURCE: Schwartz JE, Muntner P, Kronish IM, et al. Reliability of office, home and ambulatory blood pressure measurements and correlation with left ventricular mass. *J Am Coll Cardiol* 2020;76:2911-2922.

Controversy exists about which method of diagnosing and monitoring high blood pressure (BP) is best for guiding therapy to prevent end-organ damage. Schwartz et al investigated the reliability and predictive accuracy of office BP (OBP) measurements vs. home BP (HBP) vs. ambulatory BP (ABP) for predicting left ventricular mass index (LVMi) measured by echocardiography.

The study population included participants from the Detection of Hypertension (IDH) study, a community-based sample of 400 subjects without known cardiovascular disease recruited between 2011 and 2013 in New York City.[1] Exclusion criteria included BP higher than 160/105 mmHg, evidence of secondary hypertension, pregnancy, or on medications that would affect BP. The study consisted of five visits over one month with OBP, 24-hour ABP twice, HBP over three weeks, and an echo on the last visit. OBPs were attended and performed three times with three different devices (mercury, clinic oscillometric, and home oscillometric). Complete ABP studies were obtained in 91% of subjects. HBP was conducted twice one minute apart in the morning and evening, and 96% recorded at least 12 out of 28 expected readings in a week for all three weeks. All measurements were corrected for regression dilution bias, and adjustments were made for clinical features of the subjects for estimating associations with LVMi. Mean age was 41 years, 60% were women, 26% were Black, and 64% were Hispanic.

The mean awake systolic blood pressure (SBP) by ABP was 8-9 mmHg higher than the mean OBP and HBP SBPs, which were almost identical. The reliability of the first visit OBP with the subsequent visits was 0.89 and 0.85 for SBP and diastolic blood pressure (DBP), respectively. For the first week of HBP vs. the second week, it was 0.94/0.92. For the first 24-hour ABP vs. the second, it was 0.85/0.84. The corrected correlations between the three measurement techniques ranged from 0.74 to 0.89. The multivariate adjusted correlation between SBP by HBP and LVMi of 0.50 was significantly higher than those of ABP and OBP (0.43 for both; $P < 0.001$). Correlations between DBP and LVMi all were weaker, but the HBP value of 0.33 was significantly higher than the awake ABP value of 0.26 ($P < 0.05$). The three OBP equipment types produced similar adjusted correlations between SBP and LVMi (0.32 mercury, 0.39 office oscillometric, and 0.43 home oscillometric). The authors concluded HBP measurements were more reliable and more strongly associated with LVMi than OBP or ABP measurements and suggested one week of HBP monitoring may be the best way to diagnose hypertension.

■ COMMENTARY

In the Schwartz et al study, HBP involved twice-daily measurements, averaged for a week. This would tend to average out day-to-day variation and arguably would be the best estimate of basal resting BP in the subject's natural environment. OBP is well known to be problematic for several reasons. It occurs in an artificial environment. White coat hypertension is an issue. The SPRINT[2] authors worked around some of these office issues by designating a mandatory five-minute unattended (in most cases) delay before an automatic oscillometric machine measured BP. These BP measures were lower than random home measures. However, the realities of clinic practice make such measurements impractical, and this technique has not gained widespread acceptance. The availability of ABP is limited, it is poorly reimbursed, and is used rarely. Thus, the one-week HBP approach is attractive, but there are barriers to widespread use of HBP. The daily schedule will not work for everyone, although in the Schwartz et al study, 96% of subjects recorded at least 12 of the expected 28 BP readings in a week. The cost of the device is not trivial, and there is no provider reimbursement for the data review. Also, there is no infrastructure to handle the data and provide the five minutes of training required to ensure accurate data.

There were weaknesses to this study. The population studied was small, young, and had few comorbidities. Whether HBP would work as well in an older population with more comorbidities and on medications is unknown. Also, although LVMi is a valid target organ abnormality to validate the

technique's utility, Schwartz et al did not pursue long-term clinical outcomes. Surely, HBP would be more cost-effective than two or three office visits. At this point, I believe HBP is a good technique for diagnosing hypertension, but more data are needed before using it exclusively for the management of patients with known hypertension and other comorbidities. ■

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ABSTRACT & COMMENTARY

Cognitive Benefit of Rivastigmine in Parkinson's Disease Dementia with Orthostatic Hypotension

By Lynda Nwabuobi, MD

Assistant Professor of Clinical Neurology, Assistant Attending Neurologist, New York Presbyterian/Weill Cornell Medical College

SYNOPSIS: Individuals with Parkinson's disease dementia and orthostatic hypotension (OH) showed more robust cognitive improvement from rivastigmine vs. those without OH. The anti-OH effect of rivastigmine probably mediates this better response.

SOURCE: Espay AJ, Marsili L, Mahajan A, et al. Rivastigmine in Parkinson's disease dementia with orthostatic hypotension. *Ann Neurol* 2021;89:91-98.

Orthostatic hypotension (OH) is a common nonmotor symptom in Parkinson's disease (PD), with an overall prevalence of 30%, which increases to 65% as the disease progresses. Untreated, it can independently contribute to cognitive impairment in PD individuals, presumably as the result of a reduction in cerebral perfusion pressure. In individuals with Parkinson's disease dementia (PDD), the presence of untreated OH could negatively affect the efficacy of cholinesterase inhibitors used to treat PDD. Rivastigmine is approved for the treatment of cognitive impairment in patients with PDD. Using available clinical trial datasets, Espay et al tested the hypothesis that the cognitive effect of rivastigmine is not as effective in patients with PDD with OH vs. those without OH.

The authors performed a post-hoc analysis on three studies of rivastigmine in PDD in which orthostatic blood pressure measurements were recorded: a 24-week randomized, double-blind, placebo-controlled trial of patients with PDD at least two years after diagnosis; a 24-week open-label extension (a total of 48 weeks) in the same population; and a 76-week trial comparing the rivastigmine capsule vs. the transdermal patch. The main outcome was change from baseline in the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog) in patients with OH vs. patients without OH treated with rivastigmine compared to placebo. A secondary endpoint was change in Mini-Mental State Examination (MMSE) from baseline. The 76-week study used the Mattis Dementia Rating Scale (MDRS) as the outcome measure. The 24-week study was used for the main analysis because it was the only study with a placebo comparator. Statistical analysis included analysis of covariance (ANCOVA) model, with 95% confidence intervals for the difference between the treatment groups; P values were provided without adjustment for multiple comparisons.

In the rivastigmine vs. placebo study, the mean maintenance daily dose of rivastigmine for the 10 weeks preceding the study endpoint at week 24 was 8.7 mg (standard deviation [SD] = 3.4 mg); 9.8% of all OH patients were receiving OH treatment. There was a larger improvement in ADAS-Cog in the OH group at 24 weeks (5.6 ± 1.2 vs. 1.9 ± 0.9; $P = 0.0165$). MMSE also was significantly better with rivastigmine compared to placebo, but only in patients with OH (2.2 ± 4.7 vs. -0.7 ± 3.9; $P < 0.001$). At 48 weeks, with both groups on rivastigmine, the favorable effect of rivastigmine on ADAS-Cog in the OH group was attenuated (3.2 ± 2.1 vs. -1.1 ± 1.1, $P = 0.0741$). In the rivastigmine patch vs. capsule study, the daily dose during the maintenance time period ranged from 8.80 mg/day to 8.87 mg/day in patients who received the rivastigmine capsule and from 9.20 cm^2 to 9.40 cm^2 in patients who received the rivastigmine patch (10 cm^2 patch releases 9.5 mg/24 hours). At week 76, the change in MDRS was significantly better for OH patients compared with individuals without OH, but only for those on rivastigmine capsules (10.6 ± 2.9 vs. -1.5 ± 3.0 on transdermal patch; $P = 0.031$).

At the end of the 24-week study, the prevalence of OH among the patients with OH at baseline declined to 28.3% in the rivastigmine group and 44.6% in the placebo group. Of the OH-negative patients, 5% converted to OH in the placebo arm compared to 1.7% in the rivastigmine arm. Syncope was more common in the OH placebo group (9.2%) compared to the OH rivastigmine group, which included no cases of syncope.

■ COMMENTARY

Contrary to their hypothesis, Espay et al found rivastigmine produced a greater cognitive benefit in PDD patients with OH vs. individuals without OH, despite similar severity of cognitive impairment at baseline. Also, it appeared to produce a protective effect of reducing OH, given the lower prevalence at the end of the 24-week study and no episodes of syncope in the rivastigmine group. This paradoxical effect may be explained by an anti-OH effect of the medication, as seen in a related ganglionic acetylcholinesterase inhibitor, pyridostigmine, which has been shown to reduce OH. These findings suggest a potential role of rivastigmine as an adjunct treatment for OH in PD. Other researchers should conduct a subanalysis on whether treatment with OH medications contributed to the amount of cognitive improvement seen in OH patients. If this is the case, it brings up the question whether all PDD patients should be on OH medications to boost the effectiveness of cholinesterase inhibitors. ■

BRIEF REPORT

Excess Deaths During COVID-19

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

SOURCE: Rossen LM, Branum AM, Ahmad FB, et al. Excess deaths associated with COVID-19, by age and race and ethnicity — United States, January 26-October 3, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1522-1527.

Skeptics have expressed concern that mortality from COVID-19 infection is overestimated or, worse, manipulated. Compared with previous years, it is clear from national data that more people in the United States have died this year than anticipated — and not just older patients, but younger people have been affected disproportionately.

The measurement of excess deaths, as defined by the number of persons dying from all causes in excess of that anticipated for a given place and time, is useful when questions have been raised about the attribution of death to a given cause — or, in this case, the overall effect of COVID-19 on death rates in the United States. Some of this could be caused by unrecognized COVID-19 infection or an indirect effect of the pandemic on the healthcare system and the ability to receive care for other reasons.

Mortality data from the CDC National Vital Statistics System was used to examine differences in the number of deaths as defined by age and ethnicity, compared with the same weeks from 2015-2019. The percentage of excess deaths from all causes, as well as that from all deaths excluding those attributed to COVID-19, were estimated. (Expected numbers of deaths were estimated using over-dispersed Poisson regression models, accounting for seasonal trends, and also weighted for possible incomplete reporting in more recent weeks).

Compared with death data for the same weeks from prior years, nearly 300,000 excess deaths occurred in the United States between the weeks ending Jan. 26 through Oct. 3, 2020. Two-thirds were attributed to COVID-19 (n = 198,081). The remaining deaths were largely attributed to vascular events, respiratory disease, and dementia/Alzheimer's.

Excess deaths reached their highest points during the weeks ending April 11 and Aug. 8, 2020. As imagined, the lowest number of excess deaths occurred in the youngest age group (< 25 years), and the highest number of excess deaths occurred in the oldest age group (75-84 years). However, the greatest percentage change in unanticipated deaths was experienced in those 25-44 years of age (26.5%).

The percentage of excess deaths in 2020 compared with averages for the previous five years for other age groups was: 14.4% for ages 45-64 years, 24.1% for ages 65-74 years, 21.5% for ages 75-84 years, and 14.7% for ages > 85 years. The greatest percentage difference in excess deaths occurred in Latinos (53.6%), followed by Asians (36.6%), Blacks (34.6%), and American Indian/Native Americans (28.9%). In contrast, the percentage of excess deaths in whites was 11.9%. This finding is consistent with reported disparities in COVID-19 deaths in Latinos and other minorities. ■

BRIEF REPORT

Subclinical Influenza Infection in Healthcare Workers

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

SOURCE: Bénet T, Amour S, Valette M, et al. Incidence of asymptomatic and symptomatic influenza among healthcare workers: A multicenter prospective cohort study. *Clin Infect Dis* 2020; Aug 4. doi:10.1093/cid/ciaa1109.

It happens every year: Patients in the hospital for other reasons suddenly develop a fever and test positive for influenza (or respiratory syncytial virus or other viral illness). Despite all precautions, influenza vaccination, handwashing campaigns, and messaging to staff not to come to work with respiratory symptoms, healthcare workers (HCWs) are an important source of nosocomial influenza and respiratory infection. Now, it is happening with COVID-19 — employees with sniffles come to work, thinking they have a cold, only to test positive for SARS-CoV-2.

Bénet et al demonstrated just how common subclinical influenza really is in HCWs. The authors enrolled 278 HCWs providing active care at five French hospitals during the 2016-2017 winter season. Participants maintained a daily diary of symptoms and were seen for physical examination the first time in October through December before the beginning of the flu season, again in January during peak flu season, and then approximately three weeks following their second visit. Researchers obtained nasopharyngeal swabs for influenza PCR (Virocult) and serologies by hemagglutination inhibition (IHA) for influenza A H3N2- and B Victoria lineage B/Brisbane/60/2008-specific antibodies. In the event of symptoms, participants returned for an additional visit with these tests. The median age of participants was 36 years and 84% were female. Vaccine coverage was 42% for 2015-2016 and 49.6% for 2016-2017. Pauci-symptomatic infection was defined as the presence of one or more signs or symptoms for more than one day, with no fever (< 37.8°C), or the absence of cough and sore throat, whereas symptomatic influenza was defined as fever ≥ 37.8°C with either cough or sore throat. Sixty-two participants developed influenza infection during the five-month study, with a cumulative incidence of 22.3%. Impressively, 46.8% and 41.9% of these were asymptomatic and pauci-symptomatic, respectively, while only 11.3% developed more classic symptoms. Fever occurred in less than 10% of cases. At the second evaluation in January, people with confirmed influenza reported runny nose (68%), cough (64%), and headache (56%). At the third evaluation, those with confirmed influenza reported runny nose (55%), cough (45%), and headache (36%). The cumulative incidence of influenza infection did not appear to differ between those who received the 2016-2017 influenza vaccination and those who did not (20.3% vs. 24.3%; $P = 0.38$), although receipt of the 2015-2016 influenza vaccination was protective (16% vs. 27%). Working in a nursing capacity increased the risk of pauci-symptomatic or symptomatic influenza. However, work in the ICU or the presence of three or more adults in the home was associated with an increased risk of asymptomatic infection.

Nearly nine of 10 hospital staff with confirmed influenza had subclinical infection (half were entirely asymptomatic). Symptoms in 42% were atypical, with at most minor sniffles, headache, or sore throat. Attempts to keep such minimally symptomatic HCWs out of the hospital has been challenging. As our emergency room medical director said the other day, physicians still will come to work with a runny nose; they are just too important, and we do not have sufficient staff to keep everyone home with a cold. Although little can be done about asymptomatic infection, we must find a way to rapidly screen minimally symptomatic employees for subclinical serious infections, such as the flu or COVID-19. ■

PHARMACOLOGY UPDATE

Cabotegravir Extended-Release and Rilpivirine Injectable Suspension (Cabenuva) and Cabotegravir Tablets (Vocabria)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

The FDA has approved the first once-a-month, complete regimen for the treatment of HIV-1 infected adults. This regimen combines oral and injectable cabotegravir and rilpivirine. Cabotegravir is a HIV-1 integrase strand transfer inhibitor (INSTI) similar to dolutegravir. Rilpivirine is a second-generation HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI). Both the injectable combination and cabotegravir tablets received breakthrough therapy designations and accelerated priority review.[1] Oral rilpivirine was approved in 2011. Oral cabotegravir and the injectable combination are manufactured by GlaxoSmithKline and distributed by ViiV Healthcare as Cabenuva and Vocabria, respectively.

INDICATIONS

Cabotegravir/rilpivirine (CAB/RPV) should be prescribed to treat HIV-1-infected adults. This combination should replace the current antiretroviral (ARV) regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen with no history of treatment failure and no known or suspected resistance to ether CAB or RPV.[2]

DOSAGE

Treatment is initiated with a one-month (at least 28 days) oral lead-in period (CAB 30 mg and RPV 25 mg daily with a meal).[2] At month 2, administer a one-time 600 mg dose of CAB and 900 mg dose of RPV intramuscularly on the last day of the oral regimen to the ventrogluteal area (preferred) or dorsogluteal area. This is followed by 400 mg of CAB and 600 mg RPV once-monthly intramuscularly. CAB/RPV is available as a kit containing a single dose of CAB 400 mg/2 mL and RPV 600 mg/2 mL and 600 mg/2 mL and 900 mg/2 mL. CAB is available as 30 mg oral tablets. Oral rilpivirine is available as Edurant.

POTENTIAL ADVANTAGES

The extended-release formulation of CAB/RPV provides slow absorption from the injection site, resulting in prolonged elimination of the drugs. This allows for once-monthly administration. It provides another treatment option for stable, virologically suppressed HIV-1-infected adults.

POTENTIAL DISADVANTAGES

The most common adverse reaction is injection site reactions (83%), with 37% considered at least grade 2.[2] Rarely (< 1%), serious, post-injection reactions have been reported minutes after injection (e.g., dyspnea, agitation, flushing, or sweating). Eight percent of subjects reported pyrexia, and 5% reported fatigue.[2] Residue concentrations of CAB and RPV may remain in the systemic circulation up to 12 months.[2] Hypersensitivity reactions have been reported with RPV-containing regimens as well as other INSTIs.[2] Nonadherence or missed doses could result in loss of response and development of viral resistance.[2] Hepatotoxicity and depressive disorders have been reported. Monitoring of liver enzymes and depressive symptoms are recommended. Cross resistance has been observed among INSTIs and NNRTIs.[2] Drugs that are inducers of enzymes that metabolize CAB (UGT1A1 or 1A9) or those that metabolize RPV (CYP3A) are contraindicated. The injection should be administered by a healthcare professional, not by the patient.

COMMENTS

The efficacy of CAB/RPV was evaluated in two Phase III randomized, active-controlled, parallel-arm, open-label, non-inferiority trials.[2-4] Trial 1 included treatment-naïve subjects, and trial 2 included subjects with HIV-1 RNA < 50 copies/mL for at least six months on an uninterrupted standard oral ARV regimen. Acceptable ARV regimens include two nucleoside or nucleotide reverse-transcriptase inhibitors plus one INSTI, an NNRTI, a boosted protease inhibitor, or unboosted atazanavir.[4] Those taking dolutegravir/abacavir/lamivudine were excluded. In trial 1 (n = 566), subjects received a dolutegravir-containing regimen (dolutegravir/abacavir/lamivudine) for 20 weeks. Those who were virologically suppressed were randomized to CAB/RPV regimen or remained on their current oral regimen for an additional 44 weeks. In trial 2 (n = 616), subjects were randomized to the CAB/RPV regimen or remained on their current ARV regimen for an additional 44 weeks. The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA level ≥ 50 HIV-1 RNA copies/mL at week 48.

Results were 2.1% for CAB/RPV and 2.5% for standard therapy for trial 1. Trial 2 results were 1.6% and 1%, respectively. In both cases, results met the criteria for noninferiority at -10% margin.[3,4] In trial 2, three subjects experienced confirmed virologic failure in the CAB/RPV arm vs. four subjects in the standard oral therapy group.[4]

CLINICAL IMPLICATIONS

CAB/RPV provides the first once-monthly administration, complete HIV-1 treatment regimen. In the two trials, overall, 88.5% of subjects preferred CAB/RPV over daily oral therapy.[3,4] Once-a-month dosing may improve compliance, although injections require a visit to a healthcare professional. Doses of the combination injection cost $3,960 per month, plus $5,940 for the initial dose, plus any additional healthcare professional fees. ■

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CME QUESTIONS

1. **Which accurately describes a proposed mechanism for metformin to attenuate the severity of COVID-19 infection?**
   a. Reduction in hepatic glucose production
   b. Increased insulin sensitivity
   c. Reduction in thrombosis and inflammation
   d. Improved oxygenation through bronchodilation

2. **A study of various methods of diagnosing high blood pressure revealed which of these best predicted increases in left ventricular mass?**
   a. A week of home blood pressure monitoring
   b. A 24-hour ambulatory blood pressure recording
   c. SPRINT-style office blood pressure measurement
   d. Ordinary clinic blood pressure measurement

3. **In patients with Parkinson's disease and dementia, rivastigmine:**
   a. alleviates parkinsonian tremor.
   b. improves cognitive function.
   c. improves balance and gait.
   d. worsens orthostatic hypotension.

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.