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ABSTRACT & COMMENTARY

Cardiovascular Events Associated with Masked Hypertension and White-coat Hypertension

By Harold L. Karpman, MD, FACC, FACP

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

SYNOPSIS: Analysis from the Dallas Heart Study consisting of 3027 adults revealed that both white-coat hypertension and masked hypertension were independently associated with increased cardiovascular events, and, therefore, home blood pressure monitoring is recommended for U.S. adults, whether symptomatic or asymptomatic.

SOURCE: Tientcheu D, et al. Target organ complications and cardiovascular events associated with masked hypertension and white-coat hypertension. Analysis from the Dallas heart study. *J Am Coll Cardiol* 2015;66:2160-2169.

Since blood pressure (BP) readings are affected by so many factors (i.e., anxiety, body position, activities, etc.), it has been widely recognized that the office BP may not accurately reflect BPs obtained in the out of office environment.[1-3] The pattern of discordance between home and office BP readings can be divided into two major categories: white-coat hypertension (WCH), which is defined as an elevated office BP reading with normal ambulatory or home BP, or masked hypertension (MH), which is an elevated ambulatory or home BP associated with a normal office BP.[4] The cardiovascular (CV) prognosis of WCH has been controversial, even though some published studies have revealed increased target organ damage and CV complications in patients with WCH.[5-7] Other studies have revealed no significant anatomical or prognostic differences when patients with WCH were compared with a normotensive population.[8,9]

Because of the published uncertainties regarding the clinical and anatomical effects of MH and WCH, Tientcheu et al evaluated the extent of target organ complications and CV prognosis associated with

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MH and WCH in 3027 participants of the Dallas Heart Study who were followed for 9 years.[10] The Dallas Heart Study is a multiethnic, probability-based population sample of Dallas County adult residents. The study began in the year 2000 and, when evaluated, its population consisted of 54% African-Americans and 49% women, with a median age of 43 years. The same automatic oscillometric BP device was used during the in-home visits and in the office. The average of the third to the fifth BP values measured at home was recorded and used as the encounter BP both in the office and at home. Participants with WCH (3.3% of the sample) and MH (17.8% of the sample) were found to have an increased aortic pulsed wave velocity, cystatin C, and urinary albumin-to-creatinine ratio, and they were independently associated with higher CV events when compared with a normotensive group, even after adjusting for traditional CV risk factors.

■ COMMENTARY

One of the striking observations noted in this study was the significant frequency of MH occurring in 17.8% of participants overall and in 14% of those not receiving antihypertensive therapy. Whereas WCH, which occurred in 3% of the group, has been proposed to be secondary to stress-induced activation of the sympathetic nervous system during encounters with healthcare providers,[11] MH is potentially induced by mental stress at home, excessive consumption of alcohol or caffeine and/or cigarette smoking, although many other lifestyle factors may contribute to the frequency of MH.[12] The important findings demonstrating increased CV risk occurring in patients with both MH and WCH independent of CV risk factors and antihypertensive drug therapy confirms the findings of many previously published studies: Hypertension should be controlled with drug therapy, not only in the office but also in the outpatient environment. Patients must learn to properly monitor their BP at home and partner with their physician to obtain appropriate and adequate antihypertensive drug therapy and counseling as required.

In summary, clinicians should be aware that office BP readings do not provide a complete picture of a patient's BP profile because MH is so common and associated with adverse cardiovascular findings. Obviously, more research is needed in this important area. For now, consider performing home BP monitoring routinely for all adults to uncover MH patients who may require drug therapy to prevent long-term CV damage. ■

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ABSTRACT & COMMENTARY

Metformin and Colorectal Cancer Risk

By Seema Gupta, MD, MSPH

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

SYNOPSIS: In a retrospective cohort study of patients with type 2 diabetes who had ≥ 1 adenoma detected at baseline colonoscopy and a repeat colonoscopy 1-10 years later, metformin use lowered the risk of subsequent adenomas after polypectomy.

SOURCE: Marks AR, et al. Metformin use and risk of colorectal adenoma after polypectomy in patients with type 2 diabetes mellitus. *Cancer Epidemiol Biomarkers Prev* 2015;24:1692-1698.

An insulin sensitizing drug, metformin acts directly against insulin resistance and is regarded as the most commonly prescribed drug for the prevention or treatment of type 2 diabetes mellitus worldwide. Metformin, compared with other antidiabetic drugs, has been associated with cancer risk reduction in recent epidemiologic studies in diabetic patients.[1] The use of metformin in diabetic patients also has been associated with significantly lower risks of cancer mortality and incidence.[2] These analyses in patients with diabetes have found an association between metformin use and reductions in the incidence of pancreatic, liver, breast, and colorectal cancers with varying levels of statistical significance.[3] However, not all studies have found such a relationship.[4]

While colorectal cancer is the second-leading cause of cancer-related death in the United States, there remains a paucity of literature on the association of metformin use and the risk of developing colorectal adenoma. Furthermore, since many patients develop subsequent adenomas after initial polypectomy, there have been no studies examining the effect of metformin in reducing the risk of adenoma redevelopment.

Marks et al examined the relationship between metformin use and detection of new or recurrent adenomas at follow-up examination after polypectomy in patients with type 2 diabetes. Researchers conducted a retrospective cohort study of type 2 diabetes patients who were between 40 and 89 years of age. All study participants also had at least one colorectal adenoma identified at baseline colonoscopy, and at least one colorectal adenoma remaining through repeat colonoscopy up to 10 years from the baseline colonoscopy diagnosis of adenoma. The study included 2412 patients who were followed for a median of 4.5 years. Overall, 1117 (46%) patients were found to have at least one adenoma during repeat colonoscopy after the discovery of the baseline adenoma. Compared with patients not receiving diabetes medications (n = 1578), metformin-only patients (n = 457) were associated with lower adenoma recurrence risk (adjusted hazard ratio, 0.76; 95% confidence interval [CI], 0.65-0.89). Furthermore, the association between lower adenoma incidence and metformin use improved with higher total doses of metformin.

■ COMMENTARY

This study suggests a potential benefit of metformin use in lowering the risk of subsequent adenomas after polypectomy in patients with type 2 diabetes when compared with no diabetes therapy. Pre-cancerous adenomas are the most common cause of colorectal cancer. This finding suggests metformin use may confer additional benefits in lowering the risk of adenoma. There are a number of postulated mechanisms for such a benefit, including the inhibition of mechanistic target of rapamycin (mTOR) pathway and insulin-like growth factor signaling suppression.[5] However, while there is the potential for both direct antitumor effects and indirect host-mediated effects, it is important to await further research from clinical trials of metformin as an anticancer agent in the clinical setting prior to recommending it for cancer chemoprevention. It is, however, comforting to know that there may be additional benefits to an older medication, which convincingly remains the cornerstone in the management of a common disease — type 2 diabetes. ■

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ABSTRACT & COMMENTARY

Optimal Beta-blocker Dose Post-MI

By Michael Crawford, MD

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

SYNOPSIS: Investigators from the Outcome of Beta-blocker Therapy After Myocardial Infarction (OBTAIN) study hypothesized that the higher the dose of beta-blocker the lower the mortality.

SOURCES: Goldberger JJ, el al. Effect of beta-blocker dose on survival after acute myocardial infarction. *J Am Coll Cardiol* 2015;66: 1431-1441.

Taqueti VR, O'Gara PT. Beta-blocker therapy after myocardial infarction: More questions than answers. *J Am Coll Cardiol* 2015;66: 1442-1444.

Beta-blocker therapy after acute myocardial infarction (MI) was retired as a hospital performance measure because its almost universal acceptance removed its discriminating value. However, it is well known that clinically used doses are significantly lower than those achieved in the randomized trials that established their mortality-reducing benefits. Thus, the investigators from the Outcome of Beta-blocker Therapy After Myocardial Infarction (OBTAIN) study hypothesized that the higher the dose of beta-blocker the lower the mortality. The OBTAIN study was a multicenter registry that recorded beta-blocker dosing information and tracked survival. The beta-blocker and the dose were determined by the treating physician. More than 90% of the subjects were on either metoprolol or carvedilol and 91.5% of the subjects were prescribed a beta-blocker. Almost 86% were on doses < 50% of the trial target doses. After a median follow-up of 2 years, there was a 12% all-cause mortality, which was the primary endpoint. The unadjusted data showed that survival was significantly higher for any dose of beta-blockers vs no beta-blockers. The multivariate adjustment of the data showed that higher doses were not associated with better survival. In fact, the lowest mortality was observed at 25% of the target dose. The authors concluded that they had failed to demonstrate that higher doses of beta-blockers approximating those used in randomized trials improved survival compared to lower doses.

■ COMMENTARY

This retrospective, observational study tends to support what most clinicians are doing with post-MI beta-blockade: Titrate the dose to reduce the heart rate to < 70 bpm and avoid adverse effects. This practice results in reduced mortality compared to no beta-blocker use, but fails to identify an optimal dose. Most patients end up on 25% or less of the target doses achieved in the randomized trials or ≤ 50mg/day of metoprolol or ≤ 12.5 mg/day of carvedilol. Interestingly, perhaps realizing the wisdom of this approach, the various society guidelines do not recommend a particular dose. It is always nice to have a study validate what we are practicing rather than vilifying it.

Why the disconnect between the randomized trials and today's practice? The authors advanced several possibilities. First, perhaps the hypothesis is correct, but they couldn't demonstrate it in this study due to unmeasured confounders. Second, there may be a beta-blocker dose threshold and once you exceed it, you cannot show increased benefits with higher doses. Third, perhaps there is no optimal dose and it varies by patient depending on their adrenergic tone, left ventricular performance, and sensitivity to adverse effects.

Beta-blockers in the randomized trials were thought to reduce post-MI mortality by reducing ischemia, recurrent MI, and sudden death. However, these trials were conducted before widespread use of reperfusion therapy. Early reperfusion probably abrogates ischemia and re-infarction, leaving sudden arrhythmic death as the only effect left for beta-blockers. Recent studies of post-MI sudden death note that compared to the pre-reperfusion era, patients today are more likely to present with pulseless electrical activity rather than ventricular tachycardia. So widespread

beta-blocker use post-MI may be affecting ventricular arrhythmias. Recent analyses suggest that unlike the 25% reduction in death post-MI observed during the trials, beta-blocker use today reduces these endpoints by 15%, which would be at the margin of statistical significance.

The randomized trials also showed that beta-blockers were most beneficial in large ST elevation MIs or patients with reduced left ventricular performance. We know beta-blockers are good for heart failure, so with less post-MI heart failure in the current era, their effectiveness may be less. This is in line with other trends in beta-blocker use, as is pointed out by Drs. Taqueti and O'Gara. Their value in hypertension, perioperative care, and chronic stable ischemic heart disease has been questioned by recent studies. It may be that modern therapy is reducing the value of beta-blockers in cardiovascular disease. Until researchers conduct a randomized, dose-ranging trial of beta-blockers in post-MI patients in the current therapeutic milieu, we should continue doing what we are doing and not worry that we are underdosing beta-blockers in post-MI patients. ■

BRIEF REPORT

Fecal Microbiota Transplantation: Patients Need No Convincing

By Carol A. Kemper, MD, FACP

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

SOURCES: Drekonja D, et al. Fecal microbiota transplantation for *Clostridium difficile* infection. A systemic review. *Ann Intern Med* 2015;12:630-638.

Surawicz CM. Fecal microbiota transplantation: What we know and what we need to know. *Ann Intern Med* 2015;162;662-663.

Relapsing and refractory *Clostridium difficile* infection (CDI) has become a real challenge for clinicians and affected patients alike. Some patients wind up in a seemingly never-ending cycle of illness, gradual improvement, followed by a prolonged vancomycin taper, and eventual relapse. Relapse occurs in 15-30% of patients following an initial (successfully treated) episode, and further relapse occurs in > 50% of those with second or subsequent episodes. Reports of successful resolution of this nasty infection using fecal microbiota transplantation (FMT) has generated enthusiasm. But available studies vary in their approach, their timing, the frequency of treatment (single dose vs multiple doses over several days), and several guidelines now have been proposed for screening of potential donors. Some recommend FMT for those with two or more episodes, whereas the American College of Gastroenterology suggests FMT can be considered in those with three or more episodes.

Researchers performed a systematic review of the available literature related to FMT. Two randomized, controlled trials, 28 case series, and five case reports were identified for a total of 561 FMT subjects. Combining the results of the two randomized clinical trials, 27 of 36 patients treated with FMT had resolution of symptoms (75%). One of these studies administered material via nasogastric (NG) tubes, with successful resolution of symptoms in 81% at 3 months. In contrast, < 30% of patients in the two comparator arms receiving vancomycin treatment or vancomycin lavage had sustained resolution of symptoms at 3 months. In the first study, FMT was administered following 4-5 days of orally administered vancomycin (500 mg four times daily). Interestingly, 8 of the 43 patients included in this study were enrolled after their first episode of CDI. In the second randomized, controlled study, FMT was administered via NG vs colonoscopy in 20 patients, with resolution of symptoms in 60% vs 80% ($P = 0.63$). FMT was administered 3 days following completion of anti-CDI treatment.

In the various case series, researchers performed FMT in 480 patients with a history of 3-12 relapses over a 3-27 month period. Although none of these studies included a comparator arm, 85% reportedly remained disease-free following administration of FMT. In addition to these, there were seven smaller non-comparator studies for patients with refractory CDI, all using various methods, with an overall resolution rate of 55%. Symptomatic improvement was observed in 0-100%.

A third randomized, controlled trial, not published in time to be included in this analysis, demonstrated successful resolution of symptoms in 90% of patients

treated with FMT vs 26% in a vancomycin treatment group; researchers ended the study prematurely because of this substantial difference in favor of FMT.

In conclusion, FMT appears effective in approximately 55-90% of patients with relapsing and refractory CDI, and will prove a blessing to those who have been in a miserable cycle of recurrent disease. Observed side effects were minimal and included complaints of cramping, bloating, nausea, transient fever, and dizziness. One patient receiving FMT through a misplaced NG tube developed pneumoperitoneum and polymicrobial bacteremia.

Many questions remain, including who, what, and how. Various protocols are used to screen donors, and methods for administration of FMT differ. For those without access to stool, one company is marketing frozen stool from pre-screened healthy donors. I've had several enterprising patients who have tried various approaches, including small home tap water enemas mixed with stool (strained to remove the peas and carrots), to capsules stuffed with a spouse's stool, kept refrigerated, and swallowed the day following completion of orally administered vancomycin. A couple of patients have tried 10 capsules twice a day for 1-2 days, one of whom relapsed a week later, and tried it again with success. While expressing initial reluctance, patients were quick to embrace this approach following yet another relapse. One of the randomized, controlled trials above indicated that patients were initially squeamish, but when contacted 3 months later, 97% said they would do it again.

It's amazing that such a simple procedure — administration of a small amount of fecal material — can effect such an important change in your bowel flora. But that is how we develop our flora, with ingestion of fecal material from the world around us, bit by bit. As one of my favorite instructors is fond of saying, "Think of the world as covered by a thin layer of feces." ■

PHARMACOLOGY UPDATE

Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide (Genvoya)

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 a fixed-dose combination of elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) for the treatment of HIV-1 infections. TAF is a new prodrug for tenofovir, which is metabolized to tenofovir-diphosphate (TFV-DP). The fixed combination is marketed by Gilead as Genvoya.

INDICATIONS

EVG/COBI/FTC/TAF is indicated as a complete regimen for the treatment of HIV-1 infections in adults and pediatric patients ≥ 12 years of age.[1] It can be used as initial treatment or as replacement therapy for patients who are virologically suppressed. Virological suppression is defined as HIV-1 RNA < 50 copies/mL on a stable regimen for at least 6 months.

DOSAGE

The dosage is one tablet orally once daily with food.[1] Each tablet contains EVG (150 mg), COBI (150 mg), FTC (200 mg), and TAF (10 mg).

POTENTIAL ADVANTAGES

TAF provides lower plasma levels but higher intracellular tenofovir levels compared with another prodrug tenofovir disoproxil fumarate (TDF).[2] TAF may be associated with reduced renal toxicity and less effect on bone mineral density (BMD).[1,3]

POTENTIAL DISADVANTAGES

TAF is associated with greater increase in total cholesterol, LDL-cholesterol, and triglycerides.[3]

COMMENTS

The safety and efficacy of EVG/COBI/FTC/TAF was assessed in five studies.[1] Two were 48-week randomized, non-inferiority studies compared to EVGF/COBI/FTC/TDF. One study included virologically suppressed adults maintained on Atripla, Truvada + atazanavir + cobicistat or ritonavir, or EVG/COBI/FTC/TAF. A third study compared EVG/COBI/FTC/TAF to EVG/COBI/FTC/TDF in adults with renal impairment, and a fourth evaluated treatment-naïve adolescents. In the

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Clinical Briefs

By Louis Kuritzky, MD

Prostate Cancer Screening: Have Clinicians Been Listening?

SOURCE: Jemal A, et al. *JAMA* 2015;314:2054-2061.

Prostate cancer screening has been an embattled topic for more than a decade. While intuitively appealing to both the clinician population and midlife males, outcomes from large clinical trials could not confirm improvements in overall survival subsequent to screening, and, with the exception of one large trial with contentious results, data were similarly unsupportive of even reduced mortality related to prostate cancer itself. Showing how the same data can be perceived differently by different experts, the U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA) screening. The American Cancer Society endorses it in men > 50 years of age with at least a 10-year life expectancy. The American Urologic Association recommends PSA screening in men 55-59 years of age.

In 2008, the USPSTF recommended against PSA screening in men > 75 years of age, after which there was a minimal decline. Did clinicians heed the 2012 USPSTF advice to cease screening in asymptomatic men regardless of age?

Jemal et al reviewed data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population (n = 446,000) to compare PSA screening rates between 2005 and 2013. They found an 18% decline in prostate cancer screening between 2010-2013, which was independent of age and included both younger men and men > 75 years of age. Modeling methods have been published that suggest we might experience an increase in prostate cancer mortality by omission of universal screening; to date, that has not been the case, but it may require a longer window of observation before reaching definitive conclusions. ■

Potential Benefits of Down Titration Through Inhaled Steroid Discontinuation

SOURCE: Suissa S, et al. *Chest* 2015;148:1177-1183.

For patients with moderate to severe chronic obstructive pulmonary disease (COPD), combination treatment often includes anticholinergics, long-acting beta-agonists, and inhaled corticosteroids (ICS), the latter two treatments most commonly combined into a single inhalation device. As many as 85% of COPD patients are prescribed ICS, though many may fall below the threshold for ICS treatment recommended by FDA labeling or guidelines. Observational data have reported an increased incidence of pneumonia in COPD patients who used ICS, which prompts the question of whether discontinuation of ICS reduces the likelihood of pneumonia. Suissa et al used the Quebec health insurance database to evaluate a population of COPD patients who had been prescribed ICS (n = 103,386). Among this population, a comparison was made of the incidence of pneumonia in patients who continued to be treated with ICS vs those COPD patients who had discontinued ICS. The period of observation was approximately 5 years.

They found that the likelihood of serious pneumonia was reduced by 37% in patients who discontinued ICS vs those who remained on ICS. Risk reduction was demonstrated as quickly as the first month post-ICS cessation. Among ICS treatments, risk reduction was more dramatic with fluticasone cessation (42%) than budesonide (13%), but omitting either ICS was beneficial for pneumonia risk reduction. The authors suggested that ICS may be currently over-prescribed, and that limiting their use could reduce the risk for pneumonia without compromising quality of care. ■

Expanding Safe Prescribing for Metformin

SOURCE: Tuot DS, et al. *Diabetes Care* 2015;38:2059-2067.

Metformin is the pharmacologic foundation of most guidelines for management of type 2 diabetes (T2DM), based on its efficacy, safety record, and the availability of favorable clinical trial outcomes data. Although serious adverse effects from metformin are rare, significant renal insufficiency increases the risk for lactic acidosis, which can be fatal. Original FDA labeling suggested renal safety boundaries based on serum creatinine (sCR), but when first devised, the boundaries (sCR < 1.4 for women, < 1.5 for men) were based on doses of metformin up to 3000 mg/d. Currently, the maximum approved dose (2550 mg/d) is not thought to be meaningfully more efficacious than 2000 mg/d, hence the commonplace prescription of metformin 1000 mg twice a day.

Recent recommendations suggest that metformin is safe when eGFR is > 45 mL/min, but the risk rises significantly when eGFR < 30 mL/min (30 mL/min to 45 mL/min eGFR is an "indeterminate" zone). Using data from the National Health and Nutrition Examination Survey (NHANES) population (n = 3902), the investigators determined that as many as 15% of patients who were excluded from metformin based on sCR would have been eligible for metformin based on a eGFR of > 45 mL/min.

In an era of progressively more expensive interventions for T2DM, clinicians may wish to re-evaluate the boundaries of safe prescribing for metformin. ■

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first two studies, treatment-naïve subjects (n = 1733) with a mean baseline HIV-1 RNA of 4.5 $\log_{10}$ copies per mL were randomized to EVG/COBI/FTC/TAF or EVG/COBI/FTC/TDF. Virological outcome (HIV-1 RNA < 50) was 92% for the TAF-regimen and 90% for the TDF-regimen. For virologically suppressed subjects, those randomized to the TAF-regimen (n = 799) had a virological outcome of 96% at week 48 compared to 93% for those who remained on their original regimen (n = 397). Similar results were observed at week 24 for subjects with renal impairment (n = 248), for both treatment-naïve or virologically suppressed subjects. Virological outcome in treatment-naïve adolescent subjects (n = 23) was 91% at week 24. The regimens had different effect on BMD. In the parallel study, there was a mean BMD change of -1.30% from baseline for the TAF-regimen compared to -2.86% for the TDF-regimen at the lumbar spine and -0.66% compared to -2.95%, respectively, at the total hip. In the switch study, BMD at lumbar spine and total hip increased by 1.86% and 1.95%, respectively, for those switched to the TAF-regimen and showed a slight decrease (-0.11% and -0.14%) when continued on their baseline regimen. The TAF-regimen showed a 30 mg/dL increase from baseline in total cholesterol compared to 13 mg/dL for the TDF-regimen (+18.5 vs 7.8%). LDL cholesterol increased by 14.4% vs 2.8%. Triglycerides increased by 25.7% vs 8.4%.

CLINICAL IMPLICATIONS

EVG/COBI/FTC/TAF provides an alternative to EVG/COBI/FTC/TDF. Currently, the latter is one of the recommended, complete, fixed-dose regimens for initial therapy with CrCl >70 mgL/min.[5] EVG/COBI/FTC/TAF is an alternative with a potentially improved safety profile and is also approved for use in patients with CrCl > 30 mL/min. The cost of EVG/COBI/FTC/TAF is the same as EVG/COBI/FTC/TDF: $2577.66 for a 30-day supply. ■

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CME QUESTIONS

1. Compared with the normotensive group, increased cardiovascular events were observed to occur in adult subjects:

a. who were afflicted with either white-coat hypertension (WCH) or masked hypertension (MH).

b. who were afflicted with WCH but not in the MH subjects.

c. who are afflicted with MH but not in the WCH subjects.

d. None of the above

2. Based on the study by Marks et al, researchers found an association between metformin use and reductions in the incidence of:

a. colorectal cancer.

b. colorectal adenoma before polypectomy.

c. colorectal adenoma after polypectomy.

d. colorectal adenoma before and after polypectomy.