Ticagrelor appears safe if stopped 1 day before CABG

NEWS
Metformin potentially cardioprotective for T1D

RESEARCH REVIEWS
Mercaptopurine prevents postop clinical recurrence of CD in smokers

CONFERENCE COVERAGE
Same BP effect for morning vs nighttime antihypertensive dosing

FORUM
Obesity and diabetes: the slow-motion disaster
Preoperative use of ticagrelor in patients undergoing coronary artery bypass grafting (CABG) is not associated with an increased risk of major bleeding, provided the therapy is discontinued at least 24 hours before the surgery, a recent study suggests.

Current guidelines recommend that ticagrelor be discontinued 5 days before surgery, [Eur Heart J 2014;35:2541-2619; J Am Coll Cardiol 2012;60:645-681] but there are concerns that discontinuing therapy for several days may be associated with an elevated risk of cardiovascular events while waiting for surgery. [Circulation 2011;124:2610-2642]

The prospective, multicentre registry study included 786 patients (mean age 67.1 years; 132 [16.8 percent] were female) with acute coronary syndromes (ACS), who received ticagrelor with or without aspirin, or aspirin alone before undergoing CABG. One-to-one matching by propensity score yielded 215 pairs who were included in the analyses. [JAMA Cardiol 2016;doi:10.1001/jamacardio.2016.3028]

Overall, there was no significant difference in the risk of major bleeding among patients pretreated with ticagrelor compared with aspirin alone, regardless of whether bleeding grades were classified by UDPB* or E-CABG**.

Although the platelet transfusion incidence was greater among those receiving ticagrelor (13.5 percent vs 6.0 percent; p=0.009), red blood cells transfusion incidence was similar between the two groups. The risk of reoperation for bleeding was also similar in both groups.

However, patients who continued pretreatment with ticagrelor up to the time of surgery or discontinued treatment less than 2 days before surgery had a higher risk of platelet transfusion than the aspirin-alone group (22.7 percent vs 6.4 percent; p=0.008). Increased risk of major bleeding was also observed in this group of patients, as defined by E-CABG grades 2 and 3 (18.2 percent vs 5.9 percent; p=0.03) and UDPB grades 3 and 4 (22.7 percent vs 9.6 percent; p=0.06).

Among patients who discontinued antiplatelet drugs at least 2 days before surgery, platelet transfusion occurred at an incidence rate of 12.4 percent in the ticagrelor group compared with 3.6 percent in the aspirin-alone group, though this was not statistically different (p=0.22).

“Although current guidelines recommend that administration of ticagrelor should be with-
Anger, emotional upset can trigger heart attack

PEARL TOH

Being angry, emotionally upset, or having intense physical exertion may trigger acute myocardial infarction (AMI), according to the INTERHEART* study.

The case-control study analysed 12,461 patients with first AMI across 52 countries who...
ported on whether they were emotionally upset or engaged in heavy physical exertion during the 1 hour before AMI onset (case period) and during the same hour the day before (control period) through questionnaires. [Circulation 2016;134:1059-1067]

Those who reported being angry or emotionally upset within 1 hour before AMI onset were more than twice as likely to experience AMI compared with the control period (odds ratio [OR], 2.44, 99 percent confidence interval [CI], 2.06–2.89).

Similarly, engaging in heavy physical exertion during the case period was associated with more than twofold increased likelihood of AMI compared with the control period (OR, 2.31, 99 percent CI, 1.96–2.72).

Those who engaged in both physical activity and were angry or emotionally upset during the case period had further increased odds of AMI (OR, 3.05; p for interaction <0.001).

“Both [triggers] can raise blood pressure and heart rate, changing the flow of blood through blood vessels and reducing blood supply to the heart,” said lead author Dr Andrew Smyth from the Population Health Research Institute at McMaster University in Ontario, Canada, who believed that both emotional and physical triggers have similar effects on the body.

The researchers also found that the associations remained even after accounting for previous cardiovascular (CV) disease, CV risk factors, prevention medications for CV, and geographical regions.

Additionally, stratifying the analyses by age, sex, smoking status, obesity, education levels, stress levels, and medical history such as hypertension, stroke, angina, diabetes mellitus, and depression did not affect the results.

“Importantly, our findings suggest that heavy physical exertion may be a trigger for AMI, rather than any physical activity,” said Smyth and co-authors. “Therefore, clinicians should continue to recommend regular physical activity, while highlighting that short-term intense physical activity may carry a risk of triggering AMI.”

“Our findings suggest that clinicians should [also] advise patients to minimize exposure to extremes of anger or emotional upset because of the potential risk of triggering AMI,” they added.

*INTERHEART: Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries*
Obesity and diabetes: the slow-motion disaster

Excerpted from a speech by Dr Margaret Chan, director-general of the World Health Organization, during the 47th meeting of the National Academy of Medicine in Washington DC, US.

The world has 800 million chronically hungry people, but it also has countries where more than 70 percent of the adult population is obese or overweight.

Until the late 20th century, dietary issues in developing countries focused on the health consequences of undernutrition, especially stunting and wasting in children and anaemia in women of child-bearing age.

That situation has changed dramatically. In just a few decades, the world has moved from a nutrition profile in which the prevalence of underweight was more than double that of obesity, to the current situation in which more people worldwide are obese than underweight.

Once considered the companions of affluent societies, obesity and overweight are now on the rise in low- and middle-income countries, particularly in urban areas, where the increase is fastest.

In countries more recently affected by the obesity epidemic, as in the Asia-Pacific region, obesity is seen first in wealthy urban residents, and then later in impoverished rural areas and urban slums.

This shift to population-wide obesity is occurring with terrifying speed. In Mexico City, adult obesity increased from 16 percent of the city’s population in 2000 to 26 percent in 2012. By that year, 35 percent of the city’s children, aged 5 to 11 years, were obese or overweight. For the country as a whole, seven out of 10 Mexicans are now overweight, with a third of them clinically obese.

In India, the prevalence of overweight increased from 9.7 percent near the turn of the century to nearly 20 percent in studies reported after 2010.

Many other rapidly developing countries show a similar pattern. Obesity and undernutrition can occur side-by-side in the same country, the same community, even the same household.

In China, as decades of food scarcity were replaced by abundance, the prevalence of obesity and overweight more than doubled
during the last decades of the 20th century, moving from famine to feasting in less than a generation.

In 2012, China’s Minister of Health estimated that as many as 300 million Chinese were obese in a population of 1.2 billion. China, with the world’s second largest economy, now vies with the US as the nation with the largest number of overweight citizens.

Earlier this year, the *Lancet* published a pooled analysis of trends in adult body-mass index in 200 countries from 1975 to 2014. In 1974, the study estimated that 105 million adults worldwide were obese. By 2014, the number had grown to 640 million, more than a sixfold increase. This is more than half a billion people.

The analysis reached a stunning overarching conclusion. If post-2000 trends continue, the probability of reaching the global obesity target, set by WHO Member States, is “virtually zero”.

The target itself is comparatively modest: by 2025, to hold the rise in the prevalence of obesity to its 2010 level. This means, basically, to keep a bad situation from getting much worse.

And it is a bad situation, a slow-motion disaster.

Population-wide increases in body weight are the warning signal that big trouble is on its way. It takes time, but trouble eventually arrives as a wave of lifestyle-related chronic diseases.

Cardiovascular diseases are now the leading killers worldwide. In the developing world, heart attacks tend to kill abruptly, with no lingering burden on the health system.

For cancer, the most devastating diagnosis in most cultures, 70 percent of patients in resource-constrained settings are diagnosed so late that pain relief is the only treatment option. No radiotherapy. No chemotherapy. No surgery. No advanced treatments costing around $150,000 per patient per year.

Obesity contributes to the risk for cardiovascular diseases and some cancers. But the role of adiposity as an independent risk factor is strongest for diabetes. Moreover, diabetes with its costly complications, including blindness, limb amputations, and the need for dialysis, can place an extraordinary long-term burden on health budgets and household finances.

In rural parts of some Asia-Pacific countries, a diabetic can spend more than a third of total household income on the costs of care. In several countries, the costs of caring for diabetics alone can absorb 20 percent of the entire health budget.

The International Diabetes Federation estimates that the cost of caring for diabetes worldwide was at least $673 billion in 2015.

With these trends as a background, I want to make two points. First, despite multiple efforts on multiple fronts, no country in the world has managed to turn its obesity epidemic around in all age groups. Second, these trends ask us to think about what progress in the 21st century really means.

Economic growth and modernization, historically associated with better health outcomes, are actually opening wide the entry point for the globalized marketing of unhealthy foods and beverages and the switch from ac-
tive to sedentary lifestyles.

For the first time in history, rapidly growing prosperity is making many previously poor people sick. This is happening in countries with few resources and health system capacities to respond. If current trends continue, a costly disease like diabetes can devour the gains of economic development.

Diabetes is one of the biggest global health crises of the 21st century.

WHO estimates that the number of adults living with diabetes has almost quadrupled since 1980, moving from 108 million in 1980 to 422 million in 2014. More than half of these people are unaware of their disease status and even more receive no treatment.

The global prevalence of diabetes in the adult population has also increased, nearly doubling from 4.7 percent in 1980 to 8.5 percent in 2014.

No longer a disease associated with affluence, diabetes is on the rise nearly everywhere. Like population-wide obesity, its precursor, diabetes is increasing most markedly in the cities of low- and middle-income countries.

Each year, diabetes causes around 1.5 million deaths. High blood glucose contributes to an additional 2.2 million deaths, largely by increasing the risk of cardiovascular disease. That means 3.7 million yearly deaths related to high glucose levels. Of these deaths, 43 percent occur prematurely, before the age of 70.

The Asia-Pacific region is generally considered the epicentre of the diabetes crisis. In these countries, people develop the disease earlier, get sicker, and die sooner than their counterparts in wealthier countries.

In a 2015 statistics published by the International Diabetes Federation, India has nearly 70 million adults living with diabetes, with one million deaths estimated for that year alone.

In 2013, the *Journal of the American Medical Association* published a report by Chinese researchers that China has 114 million adults living with diabetes, representing a prevalence in the adult Chinese population of nearly 12 percent. Less than a third of those surveyed were aware of their condition and only a quarter reported receiving treatment.

In its most shocking finding, the study estimated that nearly half of the entire adult Chinese population has pre-diabetes, amounting to an additional 493 million people at risk of this debilitating disease, with all its costly complications.

Diabetes can be successfully managed, especially when detected early. WHO has international guidelines for doing so, including insulin and blood-glucose lowering drugs on its Model list of essential medicines.

Even better, diabetes can be prevented, ideally through population-wide interventions. Changing the environment in which people make their lifestyle choices requires extraordinary government commitment, courage, and persistence.

The *Lancet* 2015 obesity series points the finger at the international food system as the principal driver of the global obesity epidemic.

In addition, obesogenic environments are shaped by international trade policies, agricul-
tural subsidies, heavy advertising, also to children, politically powerful lobbies, and money invested to distort the scientific evidence.

When crafting preventive strategies, government officials must recognize that the widespread occurrence of obesity and diabetes throughout a population is not a failure of individual willpower to resist fats and sweets or exercise more.

It is a failure of political will to take on powerful economic operators, like the food and soda industries.

If governments understand this duty, the fight against obesity and diabetes can be won. The interests of the public must be prioritized over those of corporations.
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Mercaptopurine prevents postop clinical recurrence of CD in smokers

Postoperative thiopurine treatment appears to be justified for patients with Crohn’s disease (CD) who are smokers as mercaptopurine was recently shown to reduce clinical recurrence in this subgroup of patients.

In the multicentre, double-blind UK trial, 240 patients with CD who had undergone intestinal resection were randomized to receive oral mercaptopurine 1 mg/kg/day rounded to the nearest 25 mg (n=128) or placebo (n=112). The mercaptopurine dose was halved for patients with low thiopurine methyltransferase activity. Follow-up was for 3 years.

Fewer patients in the mercaptopurine group experienced a postoperative clinical recurrence and required anti-inflammatory rescue therapy or primary surgical intervention compared with placebo recipients (13 percent vs 23 percent), but the effect was not statistically significant (adjusted hazard ratio [HR], 0.54, 95 percent confidence interval [CI], 0.27–1.06, p=0.07). However, subgroup analyses revealed a significant reduction in postoperative clinical recurrence among patients who were smokers (adjusted HR, 0.13, 95 percent CI, 0.04–0.46) vs nonsmokers (HR, 0.90, 95 percent CI, 0.42–1.94). Previous use of thiopurines, infliximab or methotrexate, prior surgery, duration of disease and age at diagnosis did not significantly affect clinical outcomes.

The researchers suggested that smoking cessation should be considered a priority for patients with CD after surgery.

Bariatric surgery may improve work productivity among severely obese patients

Adults with severe obesity who undergo bariatric surgery maintain their working status and experience fewer health-related impairments that impact on their work, say US-based researchers.

In the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study, 2,019 nonretired adults (median age 45 years) with severe obesity (median body mass index 46) who were undergoing bariatric surgery at one of 10 medical centres in the US completed work productivity and activity impairment questionnaires prior to surgery as well as annually thereafter. Eighty percent of the patients were women.

Work status analyses were based on responses by 89 percent of the original 2,019 study participants. The prevalence of employment or disability was not significantly altered during the 3-year follow-up period. Although an increase in unemployment was noted (3.7 percent vs 5.6 percent), the researchers suggested that this was due to secular trends. Among the 1,087 employed adults who had sufficient information for inclusion in the work productivity analysis, the prevalence of absenteeism was significantly decreased, but only in the first year postsurgery (10.4 percent vs 15.2 percent). The prevalence of presenteeism (defined as work impairment due to health) was lower than baseline at all postsurgery timepoints, but did increase from postsurgery year 1 to 3, possibly due to adaptation or a decline in improvements over time.

Improvements in physical function and depressive symptoms reduced the risks of postsurgery absenteeism and presenteeism, while initiation or continuation of psychiatric treatment increased the risk. Greater weight loss was only associated with a reduced risk of postsurgery presenteeism.

Metformin potentially cardioprotective for type 1 diabetes

PEARL TOH

Metformin, a biguanide commonly used to treat type 2 diabetes (T2D), may confer cardioprotective benefits for patients with type 1 diabetes (T1D) by promoting repair and decreasing damage to the blood vessel network, according to the MERIT* study.

“For the first time, this study has shown metformin has additional benefit beyond improving diabetes control when given to patients with relatively well-controlled T1D,” said study principal investigator Dr Jolanta Weaver from the Institute of Cellular Medicine at Newcastle University in Newcastle, UK.

“This study may have positive clinical implication for patients with increased cardiovascular disease [CVD] risk by rebalancing the emphasis in their management from limiting damage alone to also improving vascular repair,” said Weaver and co-authors.

The open-label study enrolled 23 T1D patients (HbA1c <8.5 percent) without macrovascular disease or stage 3b renal impairment who received metformin in addition to their standard treatment with insulin (treatment group) for 8 weeks, 9 matched T1D patients who received standard treatment only (standard group), and 23 matched healthy controls.

At the start of the study (baseline), treatment group had lower levels of circulating endothelial progenitor cells (cEPCs) and pro-angiogenic cells (PACs), which are markers of vascular repair, and colony forming units (CFU-Hill’s colonies), a predictor for CVD risk, than healthy controls (p<0.001 for all). In contrast, circulating endothelial cells (cECs), a marker for vascular damage, were 74 percent higher in treatment group than in healthy controls (p=0.03).

After 8 weeks, markers for vascular repair (cEPCs and PACs) and CVD risk (CFU-Hill’s colonies) significantly increased in the treatment group (by >75 percent; p=0.002 for cEPCs, by 71 percent for PACs; p<0.0005 for PACs, and by 66 percent; p<0.0005 for CFU-Hills colonies) compared with baseline, to levels similar as that in healthy controls.

Metformin also significantly decreased cECs by 36 percent (p<0.05) to similar levels as that in healthy controls after 8 weeks of treatment.

In contrast, no significant changes were seen in cEPCs, PACs, CFU-Hill’s colonies, and cECs in patients receiving standard treatment after 8 weeks.
Also, no significant changes were observed in HbA1c levels and any glucose variables measured in the study, including average glucose, blood glucose standard deviation and area under the curve in all groups after 8 weeks.

“The additional benefit suggested by our study for patients with T1D is that the vascular health/repair may be improved in already well-controlled patients and without a need for further improvement in glycaemic control,” said Weaver and co-authors.

Due to the proof-of-concept design of the study, the findings could be extended to design randomized clinical trials of longer duration in the future in order to repurpose metformin for T1D patients as well, the researchers said.

*MERIT: Metformin improves Endothelial function, endothelial progenitor cells and cardiovascular Risk factors In Type 1 diabetes

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**Antidiabetic drugs as anti-HCC agents**

JAIRIA DELA CRUZ

Antidiabetic medications have potential hepatocellular carcinoma (HCC)-modifying effects that vary with each drug class, according to a network meta-analysis. Specifically, exposure to metformin or thiazolidinediones (TZDs) has been shown to be protective, whereas treatment with insulin or sulphonylurea contributed to an increased risk.

The findings may aid clinical decision making regarding appropriate antidiabetic treatment for diabetes patients with a high risk of HCC, the investigators said.

The current network meta-analysis included 13 studies and was conducted within a Bayesian framework. The total study population consisted of 481,358 diabetes mellitus (DM) patients, accounting for 240,678 HCC cases, who received at least 2 different treatment regimens.

In pair-wise comparisons, metformin reduced the risk of HCC by 51 percent (95 percent CI, 3 to 75), whereas insulin conferred a 144 percent (10 to 456) increase in HCC risk. [Sci Rep 2016;doi:10.1038/srep33743]

Metformin proved to be superior to insulin based on evidence from indirect comparisons of the included regimens. A significant risk reduction in HCC was achieved with metformin versus sulphonylurea (risk ratio [RR], 0.45; 0.27 to 0.74) and insulin (RR, 0.28; 0.17 to 0.47). Insulin, on the other hand, was associated with a marked
increase in HCC risk (RR, 2.37; 1.21 to 4.75).

“In addition, the probabilities of best treatment for each strategy suggested that metformin was the best, TZDs were the second best, sulphonylurea was the third best, and insulin was ranked the lowest in the prevention of HCC,” the investigators noted.

There was no substantial inconsistency or publication bias found in the network meta-analysis.

**Insulin-related HCC risk potentially mediated by hyperinsulinaemia**

“Our findings are consistent with the current understanding that exogenous insulin therapy or insulin secretagogues may be associated with an increased incidence of hepatoma and a higher mortality because of cirrhosis and HCC,” the investigators said.

They explained: “The administration of insulin or insulin secretagogues such as sulphonylureas, leads to exogenous or endogenous hyperinsulinaemia [which] increases hepatic growth hormone receptor levels and down-regulates the level of insulin-like growth factor (IGF)-binding protein 1, raising the bioavailability of IGF-1 on cellular proliferation and inhibition of apoptosis.”

This is also in agreement with the results of a recent meta-analysis showing that exposure to insulin and sulphonylurea led to a total of 161 and 62 percent increase in HCC incidence, respectively. [Am J Gastroenterol 2013;108:881–891]

Conversely, metformin and other insulin sensitizers may counteract insulin resistance and consequent hyperinsulinaemia and lower cancer risk as a result by inhibiting glucose uptake in the muscle, the investigators said.

Metformin may also stop the production of cancer through indirect mechanisms including “induction of cell cycle arrest and/or apoptosis, activation of the immune system, and inhibition of the unfolded protein response,” which potentially eradicates cancer stem cells, they added.

The investigators acknowledged that their analysis is limited by the inclusion of observational studies, the results of which are likely to be influenced by bias or confounding factors. Moreover, data on dosage, therapy duration, and other confounders are incomplete and therefore warrant cautious interpretation of the findings.

Additional well-designed trials and pathophysiological studies are needed to investigate the potential role and the clinical efficacy of metformin and TZDs as anticancer agents, as well as to describe the details of their biological mechanism of action, they said.
Sodium intake directly related to overall death risk

PEARL TOH

High sodium intake increases the risk of death and the amount of sodium intake is directly related to overall death rate, even at the lowest sodium levels, according to the TOHP* follow-up study.

While high sodium levels were known to be associated with an increased risk of cardiovascular disease (CVD) and total mortality, benefits of very low levels of sodium were controversial, with several studies reporting a U-shaped relationship between sodium levels and health outcomes, implying that very low levels of sodium intake could also increase overall death risk, according to the researchers.

The TOHP study was a 24-year (median duration) follow-up of participants in two trials, phase I and phase II trials in TOHP, who were randomized to either sodium reduction and lifestyle interventions including weight loss (n=3,123), or usual care (n=2,974) for 18 months and 36 months in the respective trials. Sodium levels were assessed by analysing multiple 24-hour urine samples collected during the trials. [J Am Coll Cardiol 2016;68:1609-1617]

In contrast to the U-shaped or nonlinear relationship suggested by previous studies, the researchers found a direct linear relationship between sodium levels and mortality: the risk of death increased with increasing sodium levels (hazard ratio [HR], 0.75 [for <2,300 mg/day], 0.95 [for 2,300 to <3,600 mg/day], and 1.00 [for 3,600 to <4,800 mg/day; reference] and 1.07 [for ≥4,800 mg/day]; p=0.30 for trend).

When analysed as a continuous variable, every 1,000 mg/day increase in sodium levels was associated with a 12 percent increase in mortality (p=0.052).

Additionally, for every unit increase in sodium/potassium ratio, the overall risk of death increased by 13 percent (p=0.04).

According to the researchers, the study used the “gold-standard” 24-hour urine samples for quantifying sodium levels, which was more accurate than other methods and could have contributed to different results from previous studies.

They also excluded participants with previous history of hypertension, diabetes or CVD, which might have contributed to reverse causation in the previous studies whereby these individuals reduced sodium intake due to underlying diseases, leading to seemingly increased
risk among those with low levels.

Of the 3,123 participants receiving intervention, 251 deaths occurred compared with 272 deaths out of 2,974 participants in the usual care group over the follow-up period. This translates to an overall 15 percent lower death rate in the intervention group compared with the usual care group, although this was not statistically significant after adjusting for differences in baseline characteristics.

“This finding is disappointing given the intensive nature of the dietary behavioural intervention used in the TOHP trials ... and the emphasis placed on sodium reduction in guidelines,” said Drs Nancy Cook, Lawrence Appel, and Paul Whelton from the Population Health Research Institute in Ontario, Canada, in a separate commentary. [J Am Coll Cardiol 2016;68:1618-1621] “[One] contributor to the absence of a mortality benefit may be nonadherence to dietary recommendations beyond the period of intensive intervention, although this reflects real life.”

*TOHP: Trial of Hypertension Prevention*
The timing of dosing of antihypertensive drugs (morning or night) does not affect 24-hour ambulatory blood pressure monitoring (ABPM) levels or quality of life (QoL) in patients with hypertension, the randomized crossover trial HARMONY* has shown.

“Some data from previous studies suggest that nocturnal rather than daytime dosing of antihypertensive agents may have beneficial effects on consequent cardiovascular [CV] outcomes,” said lead author Professor Neil Poulter from the Imperial Clinical Trials Unit and International Centre of Circulatory Health, Imperial College London, UK. “We sought to investigate whether 24-hour ABPM levels are consequent upon morning or nighttime dosing of BP-lowering agents.”

Twenty-four hour systolic and diastolic BP readings did not differ between patients receiving morning or nighttime dosing (129.65/77.24 vs 129.75/77.99 mm Hg, respectively). Similarly, there was no impact on mean daytime or nighttime ABPM levels, nor on clinic BP levels. Quality of life scores were also comparable for morning vs nighttime dosing (84.14 and 84.04, respectively). The results did not change despite analyses by age and gender. [ISH 2016, abstract LBOS 01-01]

“The largest difference was for nighttime systolic BP at 122.76 mm Hg for morning dosing vs 121.08 for evening dosing, which at a 1.68 difference is nowhere near statistically significant,” said Poulter. “If this was at a population level, that might be important with regard to CV events. However, in this trial, there was no sign of a significant benefit in terms of ABPMs or any other BP associated with taking your tablets in the morning or the evening.”

The trial included 103 patients (age 18–80 years) from the UK and Greece with controlled hypertension (≤150/≤90 mm Hg) and on stable treatment with ≥1 antihypertensive drug, ran-
Pharmacological approaches for optimal hypertension management

ELVIRA MANZANO

Management of hypertension is all about global cardiovascular risk management and vascular protection, says a renowned cardiologist. Blood pressure (BP) lowering is the key determinant of treatment benefit.

“Pharmacological treatment should be individualized to groups for optimal hypertension management,” said Prof Tan Ru San, cardiologist and director, Clinical Trials, National Heart Centre, Singapore. “For nonblack patients, the JNC-8 guidelines recommend a thiazide-type diuretic, a calcium channel blocker (CCB), an angiotensin converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB), alone or in combination.”

Randomized controlled trials have suggested better CV protection by including at least some nocturnal dosing of BP-lowering medications than daytime dosing. We showed in HARMONY that dosing time does not affect 24-hour ABPM levels in patients with stable BP and hypertension,” said Poulter. “The ongoing TIME [Treatment in Morning versus Evening] trial, involving 10,200 patients to be followed for 5 years, will hopefully provide definitive evidence of any preferential impact of nocturnal dosing of BP-lowering medication on major adverse cardiovascular events [MACE].

*HARMONY: Hellenic-Anglo Research Into Morning or Night Antihypertensive Drug Delivery
For black patients, initial therapy should include a thiazide diuretic or a CCB, alone or in combination, Tan added.

Guidelines recommend lifestyle modification, setting BP goals, and initiating BP-lowering medication based on age, diabetes and chronic kidney disease (CKD). In the 2013 European Society of Hypertension and the European Society of Cardiology (ESH/ESC) guidelines, the BP target is <140/90 mm Hg for hypertensive patients 18 years and older. CKD, with or without diabetes, merits initial or add-on treatment with an ACE inhibitor or an ARB, alone or in combination with drugs from other classes to improve kidney outcomes, regardless of race or diabetic status, Tan said. ACE inhibitors should not be combined with ARBs in the same patient. For uncontrolled BP or complicated cases, referral to a hypertension specialist may be necessary.

Majority of hypertensive patients with diabetic kidney disease will not progress to kidney failure, but will die from cardiovascular disease (CVD). In fact, over 80 percent of individuals with diabetes and CKD have hypertension, making BP reduction the most important strategy to reduce CVD risk.

Of note, β-blockers were dropped as a first-line choice in some hypertension guidelines because of studies showing they are less effective than other drugs for stroke protection. The American Society of Hypertension and the International Society of Hypertension (ASH/ISH) guidelines relegate β-blockers to fourth-line status [J Clin Hypertens (Greenwich) 2014;16:14-26] The Canadian and European guidelines however retain β-blockers as first-line drugs in patients younger than 80 years. [Can J Cardiol 2014;30:485-501; Eur Heart J 2013;34:2159-2219]

Aside from β-blockers, the ESH/ESC guidelines also recommend diuretics (thiazides, chlorothalidone, indapamide), calcium antagonists, ACE inhibitors or ARBs as first-line and maintenance therapies, either alone or in combination with each other. [Eur Heart J 2013;34:2159-2219]

Tan said all five drug classes were able to reduce coronary heart disease (CHD) events and stroke with similar magnitude. “β-blockers, for example, exert effects beyond BP lowering and are ideal for secondary prevention of coronary artery disease [CAD]. They also exert protective effects after myocardial infarction.” [BMJ 2009;b338:b1665]

Unlike other β-blockers, nebivolol is a highly cardioselective vasodilatory β1 blocker used in the treatment of hypertension. Nebivolol induces nitric oxide (NO)-mediated vasodilation and has the highest β1 cardioselectivity amongst β-blockers, Tan said. This means fewer adverse effects (eg, bronchoconstriction) compared with drugs that nonselectively block β1 and β2 receptors.

Given the increased armamentarium for hypertension management, selection of antihypertensive agent depends on patient-specific factors such as compelling indications, side effects, and cost. Decisions about care must carefully consider the clinical characteristics and circumstances of every patient, Tan said.
Microalbuminuria may be a sign of target organ damage in uncomplicated hypertension

ELVIRA MANZANO

Microalbuminuria is the most integrated sign of subclinical organ damage in uncomplicated hypertensive patients, according to a study presented at the ISH 2016 meeting in Seoul, Korea.

“Microalbuminuria and glomerular filtration rate [GFR] are signs of subclinical kidney damage and can independently predict cardiovascular [CV] morbidity and death,” said Dr Svetlana Villevalde of the People’s Friendship University of Russia in Russia. “So we sought to investigate whether microalbuminuria, as well as cardiac and vascular ultrasonography and carotid-femoral pulse wave velocity [PWV], has a role in hypertensive organ damage.”

The prevalence of subclinical kidney damage, left ventricular hypertrophy (LVH), carotid intima media thickness (CIMT) and/or plaque, pulse wave velocity (PWV) >10 m/s among patients in the study was 37.5, 46.3, 23.6, and 25.7 percent, respectively. Different signs of organ damage only partly clustered in the same group of patients. The odds ratio of a microalbuminuric patient developing LVH or vascular damage was 19.5, a patient with LVH having microalbuminuria and or vascular damage was 7.5, a patient with PWV >10 m/s having microalbuminuria and or LVH and or carotid thickening or plaque was 3, and a patient with CIMT >0.9 mm and/or plaque developing microalbuminuria and/or LVH and/or PWV >12 m/s was 2. (ISH 2016 meeting, abstract LBOS 01-03)

“There was a positive correlation between albumin/creatinine urine ratio and LVMI [left ventricular mass index], CIMT [carotid intima media thickness], and PWV [p<0.001 for all],” said Villevalde.

The study included 576 nondiabetic hypertensive patients without established CV or renal disease. Microalbuminuria was assessed
using albumin/creatinine urine ratio, GFR by Chronic Kidney Disease Epidemiology [CKD-EPI] Collaboration formula, as well as LVMI, CIMT, and PWV. Spearman and multiple regression analysis were performed.

“Given the availability, low cost and high predictive value of this measure, combined assessment of GFR and microalbuminuria should be the first step in the detection of target organ damage for CV assessment,” said Villevalde.

“For those with no signs of clinical kidney damage, cardiac and vascular ultrasound should be considered for assessment of LVMI and CIMT.”

1 in 5 Singapore residents has hypertension, but daily salt intake still high

PEARL TOH

Almost one in five Singapore adults aged 18–69 years had hypertension, and the dietary intake of sodium chloride (ie, salt) remained high at 8.5 g/day, which exceeded the ≤5.8 g/day intake recommended by international guidelines, revealed a study.

According to the Singapore National Health Survey (NHS) in 2010, 18.8 percent of residents aged 18–69 years had hypertension, defined as a sustained elevation in blood pressure of ≥140/90 mm Hg. [ISH 2016, abstract SSA 03-3]

When stratified into different age groups, the prevalence of hypertension increased exponentially from age 40 years onwards, with the eldest age group included in the survey (age 60–69 years) having a sevenfold greater prevalence of hypertension than those aged 30–39 years (53.4 percent vs 7.6 percent).

As salt was known to be a major contributor
to hypertension and increased risk of cardiovascular disease, Oh also drew attention to another survey, the salt intake study (SIS) 2010 within the National Nutrition Survey (NNS) conducted by the Health Promotion Board in Singapore.

Based on the 24-hour urine excretion of sodium ions in 1,182 participants included in SIS, the dietary intake of salt in residents aged 30–69 years was 8.5 g/day, which exceeded the ≤5.8 g/day salt intake recommended by the NKF KDOQI* guidelines.

When stratified by gender, men consumed 33 percent more salt than women. Also, younger adults aged 40–49 years consumed more salt (9 g/day) than older adults aged 50 years and above (7.8 g/day for those aged 50–59 years and 7.7 g/day for those 60–69 years).

However, Oh acknowledged that it was difficult to interpret the significance of a reduction in daily salt intake in older people (aged 50–69 years) as this age group also had a greater prevalence of hypertension, and some antihypertensive medications such as diuretics and inhibitors of the renin-angiotensin-aldosterone system could interfere with sodium excretion in the urine.

According to the Clinical Practice Guidelines for Hypertension released by the Singapore Ministry of Health, patients are advised to reduce their dietary intake of salt to 5–6 g/day.

"Readily accessible methods of patient prompting and education include digital apps on smartphones and tablet computers," said Oh.

In Singapore, the concerted programme of prevention and management of hypertension combines early detection via blood pressure screening for individuals aged 18 years and older, and good treatment taking into consideration the complex co-existing cardiovascular risk factors (such as obesity, diabetes mellitus, dyslipidaemia, physical inactivity, and smoking), according to Oh.

*NKF KDOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative
Older age, obesity, chronic kidney disease, and diabetes are some of the factors associated with an elevated risk for resistant hypertension, said a specialist.

“Older age and obesity ... are two of the strongest risk factors for uncontrolled or resistant hypertension,” said Dr Chia Yook Chin from the Department of Primary Care Medicine, University of Malaya, Kuala Lumpur, Malaysia. “The incidence of resistant hypertension will likely increase as the population becomes more elderly and obese,” she said. [ISH 2016, abstract SSA 03-2]

The current definition of resistant hypertension as determined by the American Heart Association (AHA), the European Society of Hypertension (ESH), and the European Society of Cardiology (ESC) is uncontrolled blood pressure (average BP ≥140/90 mm Hg) despite ≥3 optimally dosed drugs of different classes or controlled BP with ≥4 drugs of different classes (ideally including a diuretic in both cases). [Circulation 2008;117:e510-e526; J Hypertens 2013;31:1281-1357]

A study conducted in Spain found that 12 percent of the treated hypertensive population had resistant hypertension, though more than one third of this group had normal ambulatory BP. [Hypertension 2011;57:898-902] Another study from the US found that 8.9 percent of adults with hypertension have resistant hypertension. [Hypertension 2011;57:1076-1080]

“The exact prevalence of resistant hypertension in Southeast Asia is unknown. Clinical trials suggest that it is not rare and that 20 to 30 percent of study participants have resistant hypertension,” said Chia.

A study conducted in Malaysia involving 1,217 patients (mean age 66.8 years) with hypertension found that 8.8 percent of participants had resistant hypertension. Chronic kidney disease was associated with a higher risk of resistant hypertension (odds ratio [OR], 2.89,
95 percent confidence interval [CI], 1.56–5.35). [BMC Fam Pract 2014;15:131]

In a US study involving 205,750 patients with incident hypertension, 1.9 percent of whom developed resistant hypertension in a median follow-up period of 1.5 years, men, older individuals and those with diabetes mellitus had a higher risk of developing resistant hypertension. Furthermore, resistant hypertension was associated with about a 50 percent higher risk of cardiovascular events. [Circulation 2012;125:1635-1642]

A multicentre study demonstrated that resistant hypertension posed a higher cardiovascular risk than pseudoresistant or sustained hypertension (HR, 1.98, 1.24, and 1.11, respectively) compared to controls. Similarly, resistant hypertension was associated with a higher risk for renal events (HR, 2.66) compared with pseudoresistant (HR, 1.18), and sustained hypertension (HR, 2.14). [J Am Col Cardiol 2013;61:2461-2467]

With an ageing population, increasing obesity, and an increasing prevalence of chronic kidney disease due to hypertension and diabetes, we will certainly see a rise in the prevalence of resistant hypertension in Southeast Asia, said Chia.

Evaluation is crucial in order to identify resistant hypertension. “It behoves us to recognize hypertension early,” said Chia. Studies have shown that up to 50 percent of uncontrolled and resistant hypertension could be due to poor adherence, and thus identifying nonadherence is one potential way to manage this condition.

Developing countries need simplified hypertension guidelines

JAIRIA DELA CRUZ

Effective management of hypertension in developing countries warrants adoption of simplified, accessible treatment interventions adjusted to each country’s condition, inclusive of all stakeholders and with a good policy support, according to an expert.

The burden of hypertension in the less developed countries cannot be addressed solely by following “complex and largely impractical
guidelines [designed] for high-income countries,” said Dr Iwan Dakota from the Department of Cardiology and Vascular Medicine at the University of Indonesia.

Replacing these guidelines with the ones developed specifically for resource-poor settings is important as almost three-quarters (639 million) of people with hypertension live in countries with limited health resources and where people have a low awareness of hypertension and poor blood pressure control, Dakota added.

In Southeast Asia alone, hypertension strikes one-third of adults and kills 1.5 million people annually. These numbers show that a gap exists in the capacity of certain countries to prevent and control the condition, which is further exacerbated by the circumstance that Asians are at greater risk of hypertension-related diseases. [Hypertension 2007;50:991-997]

Dakota pointed out that the goal of reducing incident cases of stroke and acute coronary ischaemic events may be achieved by implementing a strong national public health campaign aimed at reducing both hypertension and its risk factors (diabetes, salt intake, and obesity), at the population and individual levels.

“Initial strategies for management involve lifestyle changes focusing on reduction of dietary salt, fat, and alcohol,” Dakota noted. “Pharmacological treatment should be initiated after lifestyle interventions, and choice of drug depends on age, the overall cardiovascular risk, and comorbidities.”

Weight management and obesity reduction, along with stress management and tobacco cessation, also play an important role, he added.

At an individual level, increasing hypertension control and reducing cardiovascular disease should include the use of primary health care as the key point of control, appointment of nurses as the main human resources to oversee diagnosis and follow-up, and adoption of a global cardiovascular risk approach to pharmacological treatment.

On the other hand, population-based approaches should include cost-effective policies for promoting tobacco control, a healthy diet targeted at reducing salt, and increasing physical activity for weight loss.

“Treatment of only patients who have a total cardiovascular risk higher than 20 percent, accompanied by a population-wide strategy to shift the cardiovascular risk distribution, seems to be the most cost-effective strategy for countries where the yearly total expenditure for health is less than $100 per citizen.”
Morning BP dipping common in treated vs untreated hypertensive individuals

JAIRIA DELA CRUZ

Silent hypotensive episodes occur with greater frequency in treated than in untreated hypertensive individuals, with the episodes tending to cluster in the morning and late morning (M/LM) hours particularly among older individuals and in the setting of uncontrolled hypertension, according to a study.

This phenomenon may be attributed to age, dosing time, and circadian decline in hormones affecting blood pressure, said one of the researchers, Dr Yonit Marcus from the Institute of Endocrinology, Metabolism and Hypertension at the Tel Aviv Sourasky Medical Center in Tel Aviv, Israel.

Marcus and her colleagues examined ambulatory blood pressure monitoring data (AMBP) from 602 hypertensive and 179 normotensive individuals.

Daytime hypotension (0600 to 2300 hours) was defined as systolic BP <110 mm Hg, as long as it was also <85 percent of the mean 24-h systolic BP. On the other hand, M/LM hypotension (0800 to 1200 hours) was defined as systolic BP <110 mm Hg or ≥25 percent lower than the mean 3 first awake AMBP recordings only if it was also <85 percent of the mean 24-h systolic BP. [ISH 2016, abstract LB0S 01-02]

In the hypertensive group, the proportion of individuals having daytime hypotension was greater among those treated with antihypertensive drugs than among untreated individuals (158/336 [43 percent] vs 76/266 [29 percent]; p<0.05). The mean daytime systolic BP during hypotension was 101 mm Hg.

Of note, there is a tendency for hypotensive episodes to cluster in the M/LM hours in nearly 50 percent (76/158) of treated hypertensive individuals with daytime hypotension versus 24 percent (19/79) of untreated hypertensive individuals (p<0.05), Marcus said.

“Clustering analysis revealed that M/LM hypotension was more prevalent, compared to other daytime hours, in treated but not in untreated hypertensive subjects (odds ratio, 1.69 and 0.87, respectively; p<0.0005),” she added.
In the subgroup of treated hypertensive individuals, M/LM clustering was observed among the uncontrolled but not in the controlled group. However, systolic BP during M/LM falls was significantly lower in controlled than in uncontrolled hypertensive individuals (93 vs 103 mm Hg; p<0.0001).

Further, treated hypertensive individuals with M/LM falls were significantly older (68 vs 64 years; p<0.0001) than treated hypertensive individuals without M/LM falls.

Meanwhile, daytime systolic BP was higher in individuals without daytime hypotension (136 vs 130 mm Hg; p<0.0001).

Age, gender distribution, percentage of diabetic individuals, number and classes of antihypertensives used, and time of medication intake did not differ between M/LM and late fallers.

“M/LM fallers had a low rate of normal nocturnal dipping,” Marcus noted.

She also acknowledged that the study has a number of limitations. One is arbitrarily defining daytime as 0600 to 2300 instead of individual patient reports. Another is not assessing data in relation to breakfast time.

“However, breakfast patterns vary considerably, and many subjects skip breakfast altogether,” she said.

Risk of CA-associated brain stroke low compared to risks linked to AF, atherosclerosis

STEPHEN PADILLA

There appears to be a very low risk of carotid stenosis-associated brain ischaemia relative to risk of stroke by the global burden of atrial fibrillation (AF) in very old treated hypertensive patients, according to a study.

For the majority of nonagenarians, researchers said that systolic blood pressure (SBP) targets of <140 mm Hg should be safe with regard to carotid stenosis.

SBP goals recommended by the US and European guidelines in elderly hypertensive patients are more substantial compared with younger patients due to an increased risk of
treatment-associated side effects and hypotension, according to researchers, adding that carotid stenosis increases with age and presents a risk of brain ischaemia if hypotension occurs.

With its relevance for the routine care of elderly with hypertension remaining unclear, researchers performed an analysis of data on precerebral artery morphology and BP evolution from a survey of aged hospitalized patients.

A total of 63 patients (aged ≥90 years; 78 percent female; 35 percent diabetics, 24 percent had AF, 41 percent had coronary heart disease) admitted to the medical ward of a primary care hospital were prospectively included over 15 months (median hospital stay 11 days). For routine assessment of cardiovascular risks, ultrasound exams of the precerebral arteries were conducted.

Researchers analysed the intima-media thickness (IMD) of the common carotid arteries (CCA) and internal and external carotid artery (I/ECA) stenosis, as well as BP (admission and discharge). Excluded were patients who died, with circulatory shock, and readmissions (n=9).

Upon admission, 76 percent of participants were on antihypertensive drugs and 43 percent had their number changed. Their mean BP was 149/88 mm Hg (36 percent SBP <140 mm Hg) versus 129/72 mm Hg at discharge (64 percent SBP <140 mm Hg; p<0.05). [ISH 2016, OS 18-02]

Their mean IMD (right/left) was 8.7/9.4 mm. Nonstenotic plaque frequencies were as follows: CCA 13/16 percent, ICA 13/16 percent, ECA 19/29 percent, bulb 62/70 percent; ICA stenosis (≥60 percent) 5/5 percent, ECA stenosis (≥60 percent) 10/19 percent, ICA occlusion 2/2 percent, bilateral ICA stenosis 2 percent (1/63); and none had bilateral ICA occlusion.

“Carotid atherosclerosis disease is omnipresent in nonagenarians,” said lead researcher Dr Jürgen Bohlender, adding that the approximately 8 percent prevalence of ICA stenosis ≥60 percent in nonagenarians matches previous estimates in younger patients aged 65 to 80 years.

“In nonagenarians treated for hypertension, the risk of hypotensive brain ischaemia by significant [carotid stenosis] appears to be low compared to the risks associated with atrial fibrillation, atherosclerosis, and embolic brain disease,” he concluded.
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The combination of exenatide and dapagliflozin improved glycaemic measures and cardiovascular (CV) risk factors in patients with type 2 diabetes (T2D) inadequately controlled with metformin, according to the results of the DURATION-8 study.

“Our findings show that, compared with treatment with exenatide or dapagliflozin alone, treatment with the drugs combined resulted in more pronounced improvements in HbA1c, weight, and systolic blood pressure – all of which are important cardiovascular risk factors,” said the study authors. The low risk of hypoglycaemia with the combination therapy was also encouraging, they said, and called for further research to determine if the combination of drugs from these two classes provides additional CV benefits compared with each drug class alone.

Exenatide plus dapagliflozin significantly reduced HbA1c levels over the 28-week study period compared with exenatide alone (between-group difference [BGD], -0.4 percent, 95 percent confidence interval [CI], -0.6 to -0.1; p=0.004) or dapagliflozin alone (BGD, -0.6 percent, 95 percent CI, -0.8 to -0.3; p<0.001). [Lancet Diabetes Endocrinol 2016;doi:10.1016/S2213-8587(16)30267-4]

There was also a significant reduction in fasting plasma glucose levels in the combination group compared with exenatide alone (BGD, -1.11, 95 percent CI, -1.55 to -0.67; p<0.001) or dapagliflozin alone (BGD, -0.91, 95 percent CI, -1.35 to -0.48; p<0.001), as well as in 2-hour postprandial glucose levels (BGD, -1.52 and -1.42; p<0.001 in combination treatment vs exenatide or dapagliflozin alone, respectively).

Patients in the combination group also experienced significant weight loss (BGD, -1.87; p<0.001 compared with exenatide alone and BGD, -1.22; p=0.002 compared with dapagliflozin alone) and reduction in systolic blood
pressure (BGD, -2.9; p=0.007 and BGD, -2.4; p=0.025 compared with exenatide or dapagliflozin alone, respectively).

The incidence of adverse events was comparable between groups (57, 54, and 52 percent in the exenatide plus dapagliflozin, exenatide alone, and dapagliflozin alone groups, respectively), with the most common adverse events across all groups being gastrointestinal events (more common in the exenatide group), injection-site nodules, and urinary tract infections.

“The safety profile was consistent with that expected from each individual agent,” said study author Professor Cristian Guja from the Carol Davila University of Medicine and Pharmacy in Bucharest, Romania, who presented the findings.

“Overall, these findings support the efficacy and safety of co-initiating exenatide and dapagliflozin in patients with T2D inadequately controlled on metformin monotherapy,” he said.

In this double-blind, multicentre (109 sites in 6 countries), active-controlled phase III trial, the researchers set out to compare the efficacy and safety of the co-initiation of the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide and the sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin versus either treatment alone.

Six hundred and ninety five adults (aged ≥18 years; mean age 54 years) with inadequate glycaemic control (HbA1c 8.0—12.0 percent despite metformin ≥1500 mg/day) were randomized to receive exenatide (2 mg once a week) plus dapagliflozin (10 mg once a day), or either drug plus a matched placebo for 28 weeks in addition to their current metformin dose.

The authors acknowledged that excluding individuals with HbA1c levels <8 percent, the lack of a placebo group, and the short study period were study limitations. However, the ongoing study extension that will take place over a 2-year period will provide long-term data on these outcomes, they said.
Semaglutide a potential option for T2D with high CVD risk

ROSHINI CLAIRE ANTHONY

Individuals with type 2 diabetes (T2D) and a high risk for cardiovascular disease (CVD) had a lower incidence of cardiovascular complications when given semaglutide compared with placebo, according to results of the SUSTAIN-6* study.

The primary outcome of the study, first incidence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke, occurred in 6.6 percent (n=108) of patients in the semaglutide group compared with 8.9 percent (n=146) in the placebo group (hazard ratio [HR], 0.74, 95 percent confidence interval [CI], 0.58–0.95; p<0.001 for noninferiority and p=0.02 for superiority). [N Engl J Med 2016;doi:10.1056/NEJMoa1607141; EASD 2016, oral presentation #S35.2]

The incidence of cardiovascular death was comparable between groups (2.7 percent [n=44] vs 2.8 percent [n=46] for semaglutide and placebo, respectively; HR, 0.98, 95 percent CI, 0.65–1.48; p=0.92) though these results were not significant.

Nonfatal MI occurred in 2.9 percent (n=47) and 3.9 percent (n=64) of those in the semaglutide and placebo arms, respectively, but these results were also not significant (HR, 0.74, 95 percent CI, 0.51–1.08; p=0.12). On the other hand, nonfatal stroke occurred in 1.6 percent (n=27) of semaglutide recipients and 2.7 percent (n=44) of placebo recipients (HR, 0.61, 95 percent CI, 0.38–0.99; p=0.04).

The rate of diabetic retinopathy complications (vitreous haemorrhage, blindness, or conditions requiring intravitreal agent or photocoagulation therapy) was higher in the semaglutide group compared with placebo (3.0 percent [n=50] vs 1.8 percent [n=29]; HR, 1.76, 95 percent CI, 1.11–2.78; p=0.02), while the rate of new or worsening nephropathy was lower in the semaglutide group (3.8 percent [n=62] vs 6.1 percent [n=100]; HR, 0.64, 95 percent CI, 0.46–0.88; p=0.005).

According to the study authors, previous studies have suggested a link between rapid glucose lowering and worsening retinopathy in individuals with type 1 diabetes. “The applicability of such an association to our finding is unclear, and a direct effect of semaglutide cannot be ruled out,” they said.

At the end of the trial, the reductions in mean glycated haemoglobin levels were -1.1,
-1.4, and -0.4 percent for individuals on semaglutide 0.5 mg and 1.0 mg, and placebo, respectively. Individuals given semaglutide also experienced reductions in mean body weight of -3.6 kg and -4.9 kg for those on 0.5 mg and 1.0 mg semaglutide, respectively. “[These reductions] may have contributed to the observed reduction in cardiovascular risk with semaglutide,” said the authors, who cautioned that the study findings may differ in other populations or with longer treatment duration.

Individuals given placebo were more likely to receive additional cardiovascular and anti-hyperglycaemic agents throughout the study period. Discontinuation of treatment due to adverse events (mainly gastrointestinal) was more common in the semaglutide group, though the rate of serious adverse events was lower in the semaglutide group than in the placebo group.

Participants in this multicentre (230 sites in 20 countries), double-blind, placebo-controlled trial were 3,297 individuals (age ≥50 years) with T2D and established CVD or chronic kidney disease (CKD) stage 3 or higher who were on standard-care therapy. They were randomized to receive either 0.5 mg or 1.0 mg of the glucagon-like peptide 1 (GLP-1) analogue semaglutide subcutaneously once a week or placebo for 104 weeks. Eighty-three percent of participants (n=2,735) had CVD, CKD, or both at baseline.
“He’s a very difficult patient!”

“What do you mean one apple a day will keep the doctor away? What’s a doctor?”

“Tell me more about this macrobiotic diet!”

“Ask not what your body can do for you. Ask what you can do for your body!”

“What kind of plastic surgeon doesn’t have a mirror!”

“Downsizing is going to take some getting used to!”

“Doctor Nzeogwu over here is part of our team of surgeons and he’ll be the anaesthesiologist during your heart bypass!”
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