

# Medical Bulletin

## News You Can Use

### Cardiovascular Disease: Study finds Best Drugs for Prevention

**A** large cohort study has identified which treatment combinations work best for people with high blood pressure at risk for heart disease/cardiovascular events. Taking both blood pressure drugs and statins might be the best choice, the researchers find.

Researchers from the William Harvey Research Institute at Queen Mary University London in the United Kingdom have recently made public the results of a large long-term study that looked at the efficiency of different treatments in keeping cardiovascular disease at bay. A combination of antihypertensive drugs and statins demonstrate the best results, the experts explain. They presented the study's results at the *European Society of Cardiology* annual congress, held in Munich, Germany, and later published the findings in *The Lancet*.



*"Patients in their mid-60s with high blood pressure were less likely to die from heart disease or stroke by age 75-80 if they had taken both calcium channel blocker-based blood pressure lowering treatment and a statin,"* explains Dr. Ajay Gupta.

The scientists derived their results from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy study, which continued the work started by the original ASCOT.

### Greetings from Blue Cross Laboratories!

*Dear Colleagues,*

*Hope all of you are in the best of health and spirit ! It gives me immense pleasure and satisfaction to present you with the final issue of the Blue Cross Medical Bulletin for this current financial year.*

*This issue will have you updated on a few recent medical discoveries/developments, and novel clinical insights involving diverse therapeutic facets. We have included a short, simple and succinct tutorial and a new segment called "Beyond the Pharmacodynamic Frontier", in which we will highlight therapeutic benefits of molecules extending beyond the realm of their current indications.*

*We hope all these topics make for interesting reading !*

*We hope you enjoy reading this edition of the Medical Bulletin as you have been in the past. Please feel free to send in your feedback, so that we can incorporate the same in future editions.*

*Happy Reading!*

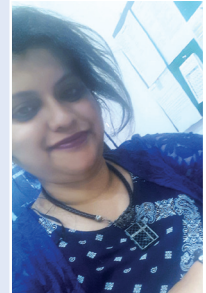
*Best wishes & Warm regards,*

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In the new study, the investigators followed 8,580 U.K. participants who were initially recruited in 1998-2000. All of the participants had high blood pressure at baseline, as well as several risk factors for developing cardiovascular disease.

The original ASCOT study had three main aims; first, to test which of two approaches to treatment — a traditional or an innovative one — would work best for preventing heart attacks. The team gave some participants the innovative therapy, which consisted of amlodipine and, if necessary, perindopril. The other participants all took the traditional treatment of atenolol and bendroflumethiazide, to which potassium was added on a case-by-case basis. **Since the novel approach proved effective in preventing strokes and premature death after a median period of 5.5 years, the researchers stopped the trial at that point.**

The ASCOT study's second aim was to see whether people with high blood pressure who also took statins would

be any more shielded against the development of coronary heart disease. The team gave this new treatment to those with hypertension and average cholesterol levels (under 6.5 millimoles per liter). On the basis of a randomized allocation, these participants took either atorvastatin or a placebo for 3.3 years. Once more, the trial was so successful in preventing heart attacks and strokes that it ended early.

Finally, the ASCOT study also aimed to assess the overall effectiveness of the two therapies for blood pressure in individuals with hypertension and high blood pressure (reading over 6.5 millimoles per liter). The researchers did not give statins to this group of participants over the 5.5 years during which they were involved in the study. Based on the ASCOT data, Dr. Gupta and team were able to assess the effectiveness of the various treatment combinations in the long-term.

**They found that the study participants who had taken amlodipine and perindopril for 5.5 years had a 29 %**

lesser likelihood of having died due to a stroke 10 years later, compared with the participants who followed the traditional therapy for blood pressure. Moreover, participants with average cholesterol levels at baseline who took a statin during the trial had a 15 % lower risk of death due to heart disease and stroke after 16 years, compared with those who only took a placebo.

Also, the participants with high cholesterol at baseline who took their usual cholesterol-lowering treatment as well as the innovative blood pressure therapy saw 21 percent fewer deaths due to cardiovascular disease over 10 years. Study co-author Prof. Peter Sever said “These results are remarkable. We have previously shown that statins confer long-term survival benefits after trials have stopped, but

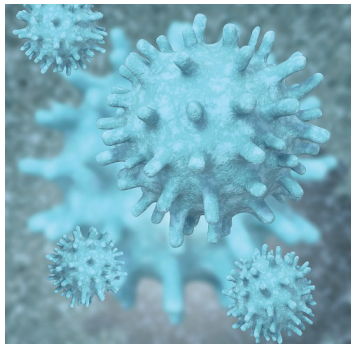
this is the first time it has been found with a blood pressure treatment.” Prof. Mark Caulfield, the director of the William Harvey Research Institute, also emphasizes the importance of the study’s findings for preventive medicine. “This study confirms the importance of lowering blood pressure and cholesterol to prevent disabling and life-shortening cardiovascular disease,” he notes.

## The Common Cold: Could we be Close to a Cure ?

The appropriately named common cold strikes the average adult two to three times per year, and children even more regularly. Currently, there is no way to prevent a common cold, and no way to get rid of it. All we can do is treat its symptoms and hold tight until it has passed.

The common cold has evaded medical science’s advances for two primary reasons. The first issue is that there is not just one single culprit. Colds are most often caused by a rhinoviruses – a large family of viruses with hundreds of variants. This makes vaccination very difficult and gives our immune system a challenging task.

Secondly, these viruses evolve rapidly – so even if we could produce vaccines to cover the full spectrum of rhinoviruses, they would quickly become resist-



ant. The common cold is an inconvenience for most of us, but can cause serious complications in people with conditions like asthma and chronic obstructive pulmonary disease.

The scientists were initially looking for a compound that would target a protein in malaria parasites. They found two likely molecules and discovered that they were most effective when they were combined. Using advanced techniques, they combined the two molecules and produced a new compound that

blocks an enzyme found in human cells, called N-myristoyltransferase (NMT).

Viruses normally steal NMT from human cells and use it to create a protective shell around their genetic information, known as the capsid. NMT is vital for the survival of cold viruses;

without it, they cannot replicate and spread. All strains of the common cold virus use this technique, so inhibiting NMT would destroy all strains of common cold virus. Also, because the molecule targets human cells rather than the virus, resistance would not be an issue.

The team’s findings were recently published in the journal *Nature Chemistry*. The researchers have high hopes for the drug, which currently goes under the codename of IMP-1088. Though other drugs that target human cells in this way have been researched before, IMP-1088 is “more than 100 times more potent” than its predecessors.

Also, earlier drugs designed to block NMT were too toxic to be of benefit. This new drug, however, did not damage cultured human cells. Of course, more research will be needed to confirm that the drug is safe for use.

So, we are not there yet, but we are close as we have ever been to a cure for the common cold.

### Short Tutorial

## Nausea & Vomiting of Pregnancy: Place of Ondansetron

Nausea and vomiting of pregnancy (NVP) is a debilitating condition affecting many pregnant women. The symptoms are usually worse in the morning (hence the name ‘morning sickness’) but can occur at any time of the day, and sometimes continue throughout the day. Up to 90% of pregnant women will experience NVP of varying severity, with symptoms gen-

erally starting around 4–9 weeks of gestation, peaking around the 7th to 12th week, and subsiding by the 16th week. The diagnosis of NVP is clinical in nature, and although other causes of persistent nausea, retching and/or vomiting are rarely encountered (gastrointestinal and/or genitourinary in nature), failure to distinguish them from NVP can result in serious complications. About

20%–30% of pregnant women will experience symptoms beyond 20 weeks, up to time of delivery.

Less than 2% of women with NVP symptoms will develop hyperemesis gravidarum (HG), characterized by protracted vomiting leading to fluid and electrolyte imbalance, nutrition deficiency and a weight loss of more than 5% of the pre-pregnancy weight, often

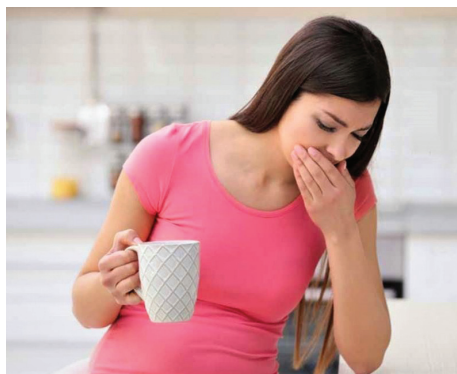


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leading to hospitalization.

Generally it has been observed that women who experience NVP have better pregnancy outcomes than those who don't, and women who use antiemetics appear to have better pregnancy outcomes than women with NVP who don't receive treatment.

Despite many theories, the etiology of NVP remains unknown. Hormonal, immunological, anatomical and even psychological contributors to NVP and HG have been proposed, although inconsistently, in many studies. Results to date remain inconclusive, as the cause is most likely multifactorial. Certain risk factors for experiencing NVP that have been proposed include decreased maternal age, increased placental mass, genetic predisposition, previous history of HG, multipara, fetal gender, and *Helicobacter pylori* infection. Women can be reassured that mild to moderate nausea and vomiting will not affect their developing baby, and is actually associated with lower rates of miscarriage, stillbirth, premature birth, intrauterine growth restriction and birth defects. However, unrelenting nausea and vom-

iting is debilitating and affects a woman's capacity to carry out her normal daily tasks. Some women may choose to terminate an otherwise wanted pregnancy.

**Management**

When symptoms persist despite lifestyle, dietary and non-pharmacological interventions (see Box), drug treatment is indicated.

**Commonly practised interventions for nausea and vomiting in pregnancy**

- Identify and avoid known triggers
- Avoid having an empty stomach
- Eat small amounts of food often
- Eat at times when less nauseous
- Avoid spicy and fatty food
- Have food and fluids at separate times
- Drink small amounts of fluids often, but try to have two litres daily
- Cold or frozen drinks and foods are often better tolerated
- Keep dry crackers and water by bedside, and eat before getting up in the morning
- Get out of bed slowly, and avoid rushing
- Herbal teas may help (peppermint, ginger)
- Do not brush teeth straight after eating
- Excess saliva can be relieved by spitting or using a mouthwash
- Rest when possible as fatigue makes nausea worse
- Acupuncture

**Ondansetron: Clinical Efficacy and Place in Treatment of NVP**

Ondansetron, a potent antiemetic agent, is a 5-hydroxytryptamine receptor 3 antagonist that blocks the effects of serotonin. It was designed originally for chemotherapy-induced nausea and vomiting. The drug is also labeled for use in nausea and vomiting associated with radiation therapy, anesthesia, and surgery. However, because there is no drug approved by the US Food and Drug Administration (FDA) for morning sickness in the United States, an increasing number of American women experiencing nausea and vomiting of pregnancy (NVP) have been treated with ondansetron.

Ondansetron is effective in treating nausea and vomiting associated with chemotherapy, which has led to its increased use in treating nausea and vomiting of pregnancy. It is the most commonly used 5-HT3 antagonist for the treatment of severe NVP, usually when other types of therapy prove ineffective. A limited number of case series and one study from Motherisk which included 176 women exposed to ondansetron in the 1st trimester, failed to find an association between exposure in first trimester and increased risk for major malformations. No increase in teratogenic risk was detected. Most observational research suggests that ondansetron is unlikely to increase the risk for miscarriage, stillbirth, or major birth defects.

**Azithromycin: A Safe and Efficacious Option for Management of Typhoid Fever**

Typhoid fever or enteric fever is a systemic illness caused by *Salmonella Typhi* and *Salmonella Paratyphi* A, B and C. It is endemic in India and is the leading cause of bacterial febrile disease in South Asia. Antibiotic therapy constitutes the mainstay of management.

Emergence of multidrug resistance (MDR) and decreased ciprofloxacin susceptibility (DCS) in *Salmonella Typhi* in South Asia had earlier rendered older drugs, including ampicillin, chloramphenicol, trimethoprim-sulphamethoxazole, ciprofloxacin, and ofloxacin, ineffective or suboptimal for typhoid

fever. However, now there has been a re-emergence of susceptibility to first-line antibiotics and a notable decline in MDR strains of *S. Typhi*.

Besides ceftriaxone, azithromycin is the recent addition to armamentarium against enteric fever. Its ability to reach very high levels at intracellular

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spaces where *Salmonella* commonly resides despite its low serum levels and high minimum inhibitory concentration (MIC) values have contributed to the good clinical response. Some publications have advocated judicious use of azithromycin as an alternative oral agent in endemic areas where DCS is common. There are also strong recommendations for azithromycin as therapy of choice until a drug susceptibility test is available.

Ideally, treatment for typhoid should be safe, of short duration (5 days), cause defervescence within 1 week, render blood and stool cultures sterile, and



prevent relapse. In a review of 20 prospective clinical trials that enrolled more than 1600 culture-proven patients, azithromycin was demonstrated to meet these criteria better than other drugs.

In a meta-analysis of randomized control trials (RCTs; 773 patients) evaluat-

ing strength of evidence supporting use of azithromycin over alternate drugs available for treatment of uncomplicated typhoid fever (chloramphenicol, fluoroquinolones and cephalosporins), it was observed that azithromycin was superior to older fluoroquinolones in reducing chances of clinical failure and relapse rate. There were no serious adverse events reported in any of the trials. Azithromycin can also be recommended as a second-line drug in MDR typhoid fever, however, large trials involving pediatric age group patients are recommended to arrive at a definite conclusion.

## Beyond The Pharmacodynamic Frontier

### Safety and Efficacy of long-term treatment with teneligliptin: Analysis of a post-marketing surveillance (PMS) of more than 10,000 Asian patients with type 2 diabetes mellitus (T2DM).

Kadowaki T, et al. *Expert Opin Pharmacother.* 2018 Feb; 19(2): 83-91.

- A 3-year PMS data analysis involving 10,532 subjects with T2DM (6,338 males, 4,194 females) demonstrated the overall safety and efficacy of teneligliptin. ADRs were reported in only 3.4% of the patients and serious ADRs in only 0.8%. The most common ADRs were hypoglycemia (0.32%) and constipation (0.27%).
- No change in mean body weight occurred, and a reduction in mean HbA1c was observed till 2 years.
- A subgroup analysis was also performed across three age groups (<65 years; 65 to <75 years; ≥75 years). The safety and efficacy profiles did not differ markedly among the three age groups.

*These interim results demonstrate that teneligliptin was well tolerated and improved hyperglycemia in patients with T2DM in clinical practice.*

### Azithromycin is non-inferior to amoxicillin-clavulanate for respiratory exacerbations in children with bronchiectasis.

Goyal V, et al. *The Lancet.* 2018; 392 (10154): 1197-1206.

- Bronchiectasis is a long-term condition where airways become abnormally widened, leading to a build-up of excess mucus that can make the lungs more vulnerable to infection. An exacerbation of bronchiectasis involves deterioration in ≥ 3 of its symptoms for at least 48 hours.
- Although amoxicillin-clavulanate is the recommended first-line empirical oral antibiotic for non-severe exacerbations in children with bronchiectasis, azithromycin is also often prescribed for its convenient

once-daily dosing.

- An international double-blind, multicentre trial assessed non-inferiority of amoxicillin-clavulanate oral suspension (22.5 mg/kg, twice daily) to azithromycin (5 mg/kg per day) in 179 children (aged 1-19 years) with bronchiectasis exacerbations.

Treatment with azithromycin was seen to be NON-INFERIOR to amoxicillin-clavulanate for resolving exacerbations in children with bronchiectasis.

In patients with penicillin hypersensitivity or those likely to have poor adherence, azithromycin provides another option for treating exacerbations.

