Current Trends in Management of Diabetes

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by

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Hippocrates Oath

I swear by Apollo, the physician, by Asclepius, by Hygeia, by Panacea, and by all the gods and goddesses, making them my witnesses, that I will carry out, according to my ability and judgment, this oath and this indenture. To hold my teacher in this art equal to my own parents, to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers, and to teach them this art, if they want to learn it, without fee or indenture. I will use treatment to help the sick according to my ability and judgement, but never with a view to injury or wrong-doing. I will keep pure and holy both my life and my art. In whatsoever houses I enter I will enter to help the sick, and I will abstain from all intentional wrong-doing and harm. And whatsoever I shall see or hear in the course of my profession in my intercourse with men, if it be what should not be published abroad, I will never divulge, holding such things to be holy secrets. Now if I carry out this oath, and break it not, may I gain forever reputation among all men for my life and for my art; but if I transgress it and forswear myself, may the opposite befall me.

Translation by William Henry Rich Jones (1817 – 1885)
Introduction

45 years of clinical practice both as Out patient consultations and In patient care including all diabetic emergencies and associated co-morbid problems / emergencies has helped to view the problem from 3 angles:

- Primary Care physician’s
- Internist’s
- Diabetologist’s
Interesting Facts

30 million people have diabetes in India 57.2 million by 2025

5th patient visiting a Consulting Physician has Diabetes

6th patient visiting a Family Physician has Diabetes

INDIA THE DIABETES CAPITAL OF THE WORLD

Diabetes Forum – Dec 2004
Cholesterol-busting wonder drugs increase diabetes risk

A comprehensive review of the available evidence shows that statins raise the risk of becoming diabetic by around 9 per cent.

Researchers warn that the absolute risk of developing diabetes remains low and is heavily outweighed by the protection from heart systems provided by the drugs.

Around 2.5 million people in Britain currently take the medication every day. Cited as a wonder drug, statins work by reducing cholesterol levels in the body, a major risk factor for heart attacks.

However, researchers have found that there was also a small increased risk of developing diabetes.

A study of cardiovascular events showed a small absolute risk for development of diabetes was outweighed by cardiovascular benefit in the short and medium term in individuals for whom statin therapy is recommended. That view was backed by diabetes and heart charities.

They warned: “In view of the overwhelming benefits of statins for revascularising the heart, the increased risk of diabetes should not stop people taking their medication.”

A rough calculation indicates that in the UK 2.5 million statin users will yield a 7% increase in diabetes cases, which is 2.5 lakhs of new diabetics every year.

India, it should be close to 2 million new diabetics every year! Who is what causes diabetes epidemic? I wonder. CUK.
Statins and risk of incident of diabetes: a collaborative meta-analysis of randomized statin trials

Summary

Background: Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. We aimed to establish by a meta-analysis of published and unpublished data whether any relation exists between statin use and development of diabetes.

Findings: We identified 13 statin trials with 91140 participants, of whom 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity ($I^2 =11\%$) between trials. Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants, but neither baseline body-mass index nor change in LDL-cholesterol concentrations accounted for residual variation in risk. Treatment of 255 (95% CI 150-852) patients with statins for 4 years resulted in one extra case of diabetes.

Lancet 2010; 375:735-42
Interpretation Station therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change.

Funding None

[www.thelancet.com](http://www.thelancet.com) Vol 375 February 27, 2010
No mention of the **load of iatrogenic diabetes** - thiazide, steroid, antidepressants, etc. particularly in the light of the recent evidence of **statin-induced diabetes** (accounting for nearly 9% of those who use this block - buster drug, whose promotional gimmicks are as subtle as they are misleading!)

At a rough estimate the incidence of new type 2 DM in the U.K. should be increasing at the rate of 2,25,000 per year if the estimated non-diabetic users of statins are around 2.5 millions! What about the effects of longterm usage of statins in diabetics and the worsening of their carbohydrate tolerance and increased anti-diabetic drug load, including the usage of thiazolidoneindiones and resultant increased cardiovascular morbidity/mortality? This is just the tip of the iceberg; why, no mention of all these in the consensus report?
Dr. M. Keshav Pai Memorial Oration, Mangalore (2008)

PITFALLS IN LINEAR DIABETOLOGY

- Diabetology as a speciality started about 50 years ago.

- Classification of Diabetologists (Prof. Sam. GP Moses)

- Origin of good control of Diabetes vs. Diabetic complications. Jean Pirat’s Retrospective analysis. The start of glucocentric tight control as the target for avoiding diabetic complications.

- The next decade; the raise of Diabetologists conclave – IDF – BDA – EASD – ADA – WHO etc.

- The Emergence of sub (super) specialities in Diabetes – Epidemiologists geneticists, Researchers (Experimental Diabetologists), Clinical Diabetologists interested in JOD, MOD, FCPD, GDM (PDG), Diabetic Foot Specialists, General, Ortho & Vascular & Plastic Surgeons, Neuro-Diabetologists, Ophthalmos / Retino Diabetologists, Dermo Diabetologists, Behavioural.(Psycho).Diabetologists etc. the list is not complete.
Comparison of syphilis & DM – Both affect all the systems in the body – know syphilis & you know medicine was replaced by know Diabetes and you know Medicine – with a difference that at this stage the medical industry (diagnostic and therapeutic support (including the nutritionists groups) found out about the tremendous future economic (money spinning) potential of – what by now became the most important ‘disease’ to affect mankind!

The rest is recent history

→ Peter Bennet’s experiments with Pima Indians linking obesity & T2DM. (Arizona USA)
→ Paul zimmet’s global trip with DM starting with Polynesian, Micronesian, Narau Islanders.
→ India the Diabetes capital of the world (WHO)
→ India as the numero uno destination for drug trials –

The cancer drug trial flop show (Johns Hopkins & Trivandrum)
Rosiglitazone fiasco with McMasters (Canada ) & Chennai.
PITFALLS IN LINEAR DIABETOLOGY

- The term Linear Diabetology is coined to denote the Obsessive Compulsive Neurosis (OCN) of both doctors and patients on the Numerical (as against clinical) control of Blood Sugars in otherwise asymptomatic and healthy persons with Diabetes.

- The Linear Diabetologist may also be labeled as a Glycaemologist or Blood Sugar Specialist as he/she apparently is utterly keen to bring the blood sugars to “normal” levels by a plethora of drugs and warns (threatens) the patients of the disasters awaiting his body and soul if he/she does not achieve “normal” Blood Sugars.&.HBA1C.values!!

- These breed of B.S.S. utterly disregard the normal and Patho physiological responses of the human body in health and ill-health and are ready to add on 1,2,3,4 drugs in their effort to subjugate the blood sugar in a Linear manner (their philosophy is simple i.e. 2+2=4 --- perhaps they are unaware of Parkinson’s Law!)

- That the human body dynamics & the therapeutic kinetics wage a war in vivo with consequences that are not fully understood and appreciated resulting in the sum total figures (+,−, ×, ÷) of the individual hormonal actions and reactions that are depicted as Blood Sugars, HBA1C, BUN, Serum Creatinine, Electrolytes, etc., is the real key to understanding diabetes control and avoiding the pitfalls of Linear Diabetology.
WHO HAS SEEN A BLOOD SUGAR?

Reflections on Medical Education

Frank Davidoff, M.D.

Who has seen the wind?
Neither you nor I;

But when the trees bow down their heads
the wind is passing by.

CHRISTINA ROSSETTI In “who has seen the wind”
The Bharatanatyam Pose captured in this illustration has been described by Dr. Padma Subramaniyam – a renowned dancer and researcher as the “FROZEN MOMENT IN THE WHEEL OF TIME”
The Story of Insulin

_In Current Medicine J.R.C.P(E)1988_

“Insulin is injected subcutaneously, not because this is an appropriate route, but because it is convenient ..... There is considerable day-to-day variation in the speed of absorption from any one site for short acting insulin and much greater variation for intermediate acting insulins. It has been calculated that up to 80% of day-to-day variation in blood glucose profiles can be explained by variation in the rate of absorption of intermediate -acting insulin.
The Story of Insulin

“Insulin Delivery to the right place at the right time” R. Taylor in Current Medicine, 1988 Journal of The Royal College of Physicians, Edinburgh.
Self Administration of Insulin – using Insulin Pen
Peter H. Forsham – M.A., M.D.
Professor of Medicine & Paediatrics; Chief Endocrinologist, Department of Medicine, Director – Metabolic Research Unit, University of California, San Francisco, USA.

Peter H. Forsham – M.A., M.D.
Meet Gladys: 83 Years and Counting

By IRL B. HIRSCH, MD

WHEN I ASKED IF SHE MIGHT LIKE TO TRY AN INSULIN PEN INSTEAD OF THE OLDER SYRINGE AND VIAL, SHE WAS QUICK TO POINT OUT WHAT SHE WAS DOING WAS WORKING, AND CHANGES OFTEN RESULTED IN PROBLEMS. AND I MUST AGREE.

June 2007 DOCNEWS
The Story of Drug Therapy (OHA) in Diabetes Mellitus

10th Congress of The International Diabetes Federation, Vienna, Austria – September 1979

A feedback study of treatment of maturity-onset diabetes (MOD) with regard to various treatment groups – Dr. C. V. Krishnaswami, Madras, India

This paper presents the results of computed analysis of 300 randomly sampled cases receiving treatment for MOD in 3 groups: Group A, diet alone; Group B, diet + oral hypoglycaemic agents (OHA), and Group C, diet + insulin. These cases were followed up regularly for 2 years, with periodic assessment of chemical control of diabetes. 32% of the cases were in Group A, 44.3% in Group B and the rest in Group C. 75% of the patients completed the 2-year follow-up. Successful chemical control was obtained in 95% of Group A (P<0.0002) and in 81 + 4.17%(mean) of Group B (P<0.02). Chemical control obtained in Group A was significantly better than in Group B or C. Group A thus acted as an ‘index group’ in the treatment of the cases under study. The skepticism regarding the hypoglycaemic effects of OHA is perhaps because the studies so far published do not have the result in the index group, as obtained in this study. Only such a type of diet could be expected to give sustained good results in the treatment of MOD, when OHA are indicated.
The Story of Biguanides – Phenformin & Metformin

Phenformin

LACTIC ACIDOSIS FOLLOWING PHENFORMIN THERAPY
(A review of authors’ experience in 25 Indian diabetics)

By

C.V. KRISHNASWAMI* and K.VALMIKINATHAN**

It is difficult to make any definite conclusions based on this limited study. At the same time, it is quite speculative that these rather subtle changes in anion gap are perhaps indicative of the early phase of Phenformin effect. This may well be a physiological adaptation to possibly a type of drug induced stress leading to sodium retention. This possibly has to be entertained in view of the report of Phenformin impairing \( \text{NH}_4^+ \) formation which is quite often implicated in sodium exchange (Rooth and Bandman, 1973).


JOUR. DIAB. ASSO. IND. : VOL XIX. IAN, 1979
Biguanides – Metformin

We in India have used it for the past 50 years, as did physicians and diabetologists in Europe & U.K.

In 1970s complications were reported with Phenformin like Lactic acidosis and the findings of UGDP study findings that it increased Na, BP and caused fatal stroke, causing premature withdrawal of the drug from the trial – all these brought to the fore Metformin which was claimed to be 10 times less toxic than Phenformin in producing L.A still it took 20 more years for the FDA to allow Metformin into the U.S Market, immediately followed by mega hype on its various beneficial effects.
Contraindications to the use of Metformin

Evidence suggests that it is time to amend the list

Suggested revised contraindications and guidelines for withdrawing Metformin

- Stop if serum concentration of Creatinine is higher than 150 micromols/L.*
- Withdraw during periods of suspected tissue hypoxia (for example, due to myocardial infarction, sepsis).
- Withdraw for three days after contrast medium containing iodine has been given, and start treatment with Metformin only after renal function has been checked.
- Withdraw two days before general anaesthesia and reinstate when renal function is stable.
- Any concentration of Creatinine that is chose as a cut-off point for renal failure will be arbitrary in view of individual patients’ muscle mass and protein turnover, and caution should therefore be used in prescribing Metformin for elderly patients.

* BMJ 2003;326:4-5 (4 January)
Cost-Effectiveness of Lifestyle Modification and Metformin Therapy in Preventing Type 2 Diabetes

A three-year study of 3,234 people in the Diabetes Prevention Program (DPP) age 25 or more who had impaired glucose tolerance and fasting glucose levels of 95–125 mg/dl. Participants were randomly assigned to receive placebo, modify their lifestyle (getting 150 minutes of activity per week) and achieve a 7% weight loss, or receive 850 mg of metformin twice a day.

<table>
<thead>
<tr>
<th></th>
<th>Lifestyle</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in development of diabetes*</td>
<td>11 years</td>
<td>3 years</td>
</tr>
<tr>
<td>Reduced incidence of disease*</td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td>Cost</td>
<td>$1,100 (per QALY)</td>
<td>$31,000 (per QALY)</td>
</tr>
</tbody>
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*compared with placebo
QALY (quality-adjusted life year)


This issue of the *Professional Section Quarterly* was provided as a professional courtesy by Pfizer Inc.
The Story of Glitazones – (Thiazolidinediones)

1. Troglitazone (Rezulin):

This exciting PPAR Gamma Activator Agent, was approved by the US FDA and began being used clinically in 1997 and after causing irreparable Liver Damage to Significant number of patients, was withdrawn from the market in early 2000.

The US federal Government Healthcarers are still paying for the treatment of patients with irreversible liver failure caused due to Troglitazone. The story behind the story was what happened in the lower / higher echelons of the US FDA (reported in BMJ / NEMJ).
Diabetes Recall

Though Rezulin’s withdrawal is a blow for some patients, there are ways to cope. Here’s how

I often think of the first couple of years after a drug has been approved as its guinea-pig period. After all, even the most careful clinical trials of a new medication usually involve just a few thousand patients. So, in the beginning, only a drug’s most common side effects are known. But once a pharmacological is cleared by government regulators, hundreds of thousands, if not millions, of people start taking it. That’s when you get a better idea of the true rate of complications, as well as any untoward interactions with other drugs.

Consider what happened with Rezulin, the diabetes drug that was taken off the market in the U.S. last month. The Food and Drug Administration approved the medication in 1997 after tests on 3,000 people showed that it could help control Type 2 (formerly adult-onset) diabetes, which affects 15 million Americans. Although some test subjects developed abnormal liver reactions, no one suffered permanent damage, and no one died. Now that millions have taken Rezulin, however, it has been linked to at least 90 cases of liver failure, 63 of which resulted in deaths.

When serious complications first started showing up, the FDA strengthened the warning labels on Rezulin and recommended regular liver tests for all patients using it. But not everyone got tested, and it was impossible to predict who would suffer a bad reaction. Then last year the FDA approved two new drugs (Actos and Avandia) that are chemically related to Rezulin but appear to be safer. Rezulin began looking like more trouble than it was worth.

All three drugs work by boosting the body’s response to insulin. Unlike folks with Type 1 diabetes, those with Type 2 usually produce their own insulin. “Type 2 is more of a supply-and-demand problem,” says Dr. David Nathan, a diabetes expert at Massachusetts General Hospital in Boston. The body can’t keep up with its elevated need for insulin, and it becomes more and more resistant to the insulin it does make. Rezulin was the first drug that directly lowered insulin resistance.

Some critics have argued that the FDA waited too long to ask Warner-Lambert, the manufacturer, to issue a recall. The pharmaceutical company still believes Rezulin is a good drug and blames the media for sensationalizing its risks. But what the people currently taking Rezulin need to know right now is how to get off the drug without jeopardizing their health.

They shouldn’t go cold turkey on their own; their diabetes could slip out of control. And those people who rely on supplemental insulin, may need their doctor to adjust their dose. There are many people who have been put on one of the new alternatives. Doctors rely on several other medications to treat Type 2 diabetes. “I personally have been very cautious about prescribing the new drugs,” Nathan says. Besides, Actos and Avandia also require precautionary liver tests.

It may be possible to beat insulin resistance through lifestyle changes. Losing weight, if you’re overweight, is a start. But even for those who have trouble dropping the pounds, getting more exercise and adding whole grains to your diet can lower your insulin resistance and decrease your need for medication. No one ever said treating diabetes is easy, but there are a lot of people who can do it and keep their blood sugar under control.

By Christine Gorman

For more information on Rezulin or diabetes, visit time.com/personal. You can e-mail Christine at gorman@time.com

Good News

Powerful Predictor

Had your high-sensitivity C-reactive protein tested lately? Maybe you should, even if you’ve never heard of it. Its presence indicates inflamed arteries, and researchers report that it may be more strongly linked to heart attacks than cholesterol. A study of 28,000 healthy women found that those with high blood levels of hs-CRP (as your doctor calls it) are 4.5 times as likely to suffer a heart attack or stroke even if their cholesterol count is normal. The test for hs-CRP is inexpensive and has been approved for use since late last year.

Not Just for Dogs

Finally, a broad look at whether glucosamine and chondroitin—two widely popular arthritis treatments first used for gory dogs and horses—really work on humans. Analysis of eight trials involving 1,500 people confirmed that a daily dose of 1,500 mg of glucosamine or 1,200 mg of chondroitin relieves arthritis pain more effectively than a placebo, with chondroitin edging glucosamine by a nose. Don’t get too frisky, though: larger and larger studies are still needed.

Bad News

Mother Load

When Mom’s blue, the kids feel it. And psychologists who studied 85 families have discovered another fascinating consequence of a mother’s mild-to-severe depression: daughters may go into puberty early. That also seems to happen to their non-human male, like stepfather, joins the family. No one knows why, but it’s thought that stress hormones and other chemicals play a role.

Hidden Cepex

Think you don’t have herpes? Well, you might. Researchers have found that two-thirds of those who turn out to be positive for the virus on a blood test have no idea they’re infected, in part because their lesions are not as obvious. But the ones with full-blown oozing blisters, they still shed the virus—and can infect others. If you’re worried, use a condom and get a blood test.

By Janice M. Horowitz

New England Journal of Medicine (3/23/00)
City Institute to take part in diabetes prevention project

The six-year project - Diabetes Reduction Assessment with the drugs, Ramipril and Rosiglitazone, is in coordination with the McMaster University, Canada, with partial funding of the Canadian Government.

The Hindu, Sunday, July 1 2001 Page 3
The wonder drug that wasn’t

By C.V. Krishnaswami

Diabetes mellitus (the adult-type or Type 2) is indeed common in our country with an age-standardised prevalence of about: 2.53 per cent for all ages; 0.62 per cent for 0-20 years; 4.16 per cent for those over 20 years; and 9.25 per cent for those above 40 years and above, as was revealed in a study conducted by our department in collaboration with the National Institute of Epidemiology.

I would like to say that this would mean that there are about four per cent of the population above the age of 20 years and nine per cent of those above 40 years would have known diabetes. In this population, if tested by the oral glucose tolerance test, we could diagnose impaired glucose tolerance (IGT) which is borderline diabetes, in a high percentage of persons (up to 25 per cent as was shown in a study conducted by our department on the IIT campus for two years and published in the Journal of Association of Physicians of India, November 1999).

The study also showed that after one year of follow up of these IGT cases, with monthly counselling by our team on diet, exercise, and lifestyle modifications, 64.3 per cent of these cases reverted to normal without resorting to any drug therapy and 30.2 per cent remained status quo, while 5.5 per cent of the IGT cases progressed to frank diabetic state.

The important questions therefore are:

(a) whether drug intervention is prima facie justified in trying to postpone or prevent the possible progression of this small percentage of IGT cases (i.e. for the questionable benefit of five per cent we have to treat all the 100 per cent).

(b) whether these drugs used over the six-year period of study planned by a Canadian agency are safe and without serious side effects? I would like to draw the attention of all diabetologists and the public to the report in the Time magazine (April 17, 2000) titled ‘Diabetes Recall’ (page 50). The drug in question which was approved rather hastily by the FDA in January 1997, was Rezulin or Troglitazone and was withdrawn in March 2000 on account of causing irreversible liver damage in an unacceptable large number of people treated with this; also there are some reports regarding the role of the drug company in playing down the potentially fatal risks associated with Troglitazone during the approval process.

(Continued on page 12)

THE HINDU, Thursday, July 5, 2001 11

**OPINION**

by the FDA in the U.S. (British Medical Journal, March 24, 2000).

(c) The drug, Rosiglitazone, that is being planned to be used in the diabetes prevention trial by three well-known institutes — Madras Diabetes Research Foundation, Chennai; St. John’s Medical College and M.S. Ramaiah Medical College (both in Bangalore) — in collaboration with the McMaster University, Canada, for a six-year period, is a modification of Troglitazone which has been withdrawn. It has to be used with great caution particularly in Indian subjects who are prone to a variety of liver ailments including due to nutritional, viral, amoebic and various other causes not to mention alcohol abuse and its effects.

Dr. David Nathan, a top diabetologist from Boston is quoted as saying: “I have been very cautions about prescribing the new drugs”. He was referring to Rosiglitazone and its sister drug Pioglitazone. Besides both these require regular monitoring of liver functions. While these group of drugs require careful monitoring by experts even in the treatment of full-fledged diabetics, it looks rather dangerous to embark on a long-term study on human subjects (with borderline diabetic curve and no symptoms) without adequate knowledge (or) evidence of its long term ill effects on the liver.

(d) Our study has shown that 95 per cent of the IGT cases do not progress to frank diabetic state if properly counselled and they do not require any drug therapy; this percentage could be increase even more if diabetes educational inputs (using modern methods such as the Internet postal in various languages) are made available to the people all over the country. As such I feel constrained to question the ethical/moral propriety of drug intervention over a six-year period, using compounds whose long-term track record is not yet known fully, and the predecessor drug of the same group was withdrawn after usage for only three years with documented irreversible liver failure cases.

The other question, to be asked is, whenever such drug trials are conducted with international agencies, whether these are done after obtaining approval from a suitable Government committee as it involves public health and welfare. Also to be taken into account are the funding agencies and their competing interest in the project.

Lastly why does a drug trial planned for the next six years, need so much publicity in the ‘lay press’ even before the start, if the results are to be unbiased?

The second drug Ramipril mentioned in the study is an expensive cardiological agent and to use this over many years on borderline asymptomatic IGT patients for possible prevention or postponement of ‘diabetes’ would certainly not benefit the patient, but probably ringing in millions of dollars to the manufacturer’s kitty.

(The writer is Head, Diabetes Department, VHS Medical Centre, Chennai.)
Diabetes drug with little side-effects

Dr. V. Mohan, Director, Madras Diabetes Research Foundation, Chennai, and Dr. Salim Yusuf, Director, Division of Cardiology, and Dr. Hertzel Gerstein, Director, Division of Endocrinology, McMaster University, Hamilton, Canada, write:

This is in response to the news item “The wonder drug that wasn’t (The Hindu, July 5) to set the record straight.

The Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication (DREAM) is an international study which has undergone extensive peer reviews by several international bodies including the Canadian Institutes for Health Research and other scientists in the U.S., the U.K., Australia, and several European and South American countries. The trial has been approved by the Food and Drug Administration (FDA) in the U.S. and the Health Protection Branch of Health Canada for conduct in these countries. Thus the DREAM study has received extensive scrutiny, review and approval.

Dr. C. V. Krishnaswami of the VHS Medical Centre, Chennai, has unfortunately extrapolated the side-effects of Troglitazone to a different compound that we are using in the trial, namely Rosiglitazone. It is indeed true that Troglitazone was banned due to liver toxicity. But precisely for this reason, Rosiglitazone an Pioglitazone the next generation drugs of this new class of insulin sensitizers have been very carefully and extensively evaluated in clinical trials across the world to ensure their safety and efficacy. Rosiglitazone is now available worldwide and till date there have been no reports of liver toxicity with this drug although several million prescriptions have been dispensed. In India, several drug trials were conducted before the drug was marketed. It has been the experience of diabetologists all over India that many patients whose diabetes could never be controlled well are now main-
taining excellent control after addition of this drug. Until now, there has not been any report of liver toxicity due to this drug in India although several thousand patients are using the drug. The only side-effects reported are weight gain and mild swelling of feet in some patients both of which are dose related and reversible if the drug is withdrawn. Rosiglitazone, and the insulin sensitizers in general, address the core defect in diabetes, namely insulin resistance; and hence it makes sound physiological sense to use these drugs early in the course of the disease, namely at the stage of impaired glucose tolerance to try to prevent diabetes. The DREAM study is an attempt in this direction.

Ramipril prevented strokes

Regarding the other drug, Ramipril, Dr. Krishnaswami is right in saying that it is primarily an anti-hypertensive agent and his comments were probably justified before the HOPE trial. But in the light of the landmark HOPE trial which showed that Ramipril actually prevented diabetes (although it was not an expected end-point of that trial), the DREAM study assumes great significance. It is well-known that subjects with impaired glucose tolerance (inability to handle a glucose load appropriately, but no diabetes) are at the same risk of developing cardiovascular complications as subjects with diabetes. In the HOPE study, Ramipril prevented heart attacks, strokes and cardiovascular-related deaths in both diabetics and non-diabetics with previous cardiovascular disease. Thus, irrespective of whether Ramipril prevents diabetes or not, it could definitely be expected to reduce cardiovascular morbidity and mortality in the study particularly since IGT subjects are known to have significantly higher prevalence of hypertension. If the study eventually proves that by using one drug one can prevent dia-

betes, control BP and reduce cardiovascular morbidity and mortality, it would indeed be a “DREAM” come true.

It is a tribute to India that for such a landmark study, Indian diabetologists have also been invited to take part. Whenever a new trial is taken up, it tries to answer unsolved questions and thus improve the lives of patients. Dr. Krishnaswami himself states that 5.5 per cent of IGT developed diabetes every year in his study.

A simple calculation will reveal that this works over to 55 per cent conversion to diabetes over a 10-year period. In fact, several studies now suggest that Indians with IGT probably develop diabetes at a faster rate than other ethnic groups. Given the millions of people at risk of developing diabetes in India, nowhere are prevention studies more relevant than in India.

Needless to say, the study will have to be reviewed and approved by the Ethical Committees of all three institutions participating in the trial and all necessary regulatory permissions will have to be obtained before it is implemented in India. Further, an independent international Data and Safety Monitoring Committee consisting of eminent scientists and physicians will carefully monitor all aspects of the study. This provides a high level of oversight and protection for the participants in the study.

No progress can be made in the field of medicine without trying out newer methods of treatment. In this case, the study does not involve any experimental drugs but is merely an extension of the use of two well-established drugs for a new indication — to try to prevent diabetes itself. If, at the end of the study, we have been able to prevent diabetes and/or prevent cardiovascular morbidity and mortality, we would consider our efforts to have been worthwhile.
Issues concerning ‘wonder drug’

Dr. C.V. Krishnaswami, Head of the Diabetes Department, Voluntary Health Services (VHS), Chennai, writes:

On July 1, The Hindu published a news item ‘City institute to take part in diabetes prevention project’ (Chennai city edition Page 3). It raised some important questions relating to the ethical and medical aspects of drug intervention studies in the prevention of a symptomatic impaired glucose tolerance stage of diabetes and the need to monitor these by an independent body of experts, familiar with our people. The National Academy of Medical Sciences (which is a constitutionally-created apex body of medical scientists) is one such. My viewpoint was published unabridged by The Hindu on July 5, under the title ‘The wonder drug that wasn’t’ (Page 11). In my write-up I had not mentioned the names of any person or institution.

After a gestation of three weeks, Dr. V. Mohan, Director, Madras Diabetes Research Foundation, Chennai, and Dr. Salim Yusuf, Director, Division of Cardiology, and Dr. Hertzel Gerstein, Director, Division of Endocrinology, McMaster University, Hamilton, Canada, presented their viewpoint “to set the record straight”. This was published in The Hindu on July 26 (Page 13), where my name was repeatedly mentioned. I do not wish to enter into an argument, at any personal or institutional level, on what has been said by them. But the three writers have not answered any of the following points:

1. The medico-moral issue of using chemical compounds on a long-term basis for a long number of years on symptom-free individuals with borderline glucose tolerance (IGT) test abnormality in laboratory tests; (2) Drugs that have been in clinical use on patients for about three years in a study spanning for more than six years; (3) The medical wisdom in the choice of the drugs; (4) The use of statistics to create panic in the minds of the public is to be abhorred. I had quoted a study where 5.5 per cent IGT cases became diabetic in the one-year study period, and also noted that 64.3 per cent of the same group which had IGT became normal and 30.2 per cent remained status quo, during the same period.

To extend this number unilaterally to the diabetes conversion alone with simple arithmetical jugglery is not scientific and contrary to medical statistical principles; (5) There is a need for an autonomous statutory national committee of experts — e.g., the ethics committee of the National Academy of Medical Sciences — to clear such drug trials affecting the lives of a large number of people; and (6) and the funding agencies involved and their competing interests.

I have been in clinical practice of diabetes, research and education for three-and-a-half decade and fully support progressive initiatives in clinical research in diabetes. At the same time, the medical profession should bear in mind the oath of Hippocrates that we should do no harm to patients by our actions.

I would leave it to the medical intelligentsia and the enlightened readers of The Hindu to decide whether the points raised by me have been answered by the three medical men. Generally, people live on, because of the hope and dreams, and sometimes in spite of them!
Rosiglitazone: Increased Risk of Heart Attacks

It has now known that rosiglitazone, as compared to other agents, is associated with significant increase in the risk of myocardial infarction and risk of death from cardiovascular causes. The conclusions are based on meta-analysis of 42 randomized, comparator trials involving 27,843 patients. The mechanism for the increased risk may be due to adverse effect of rosiglitazone on lipids, particularly increase in low density lipoprotein (LDL) by 18.6 percent. Other factors could be the drug’s propensity to precipitate congestive cardiac failure and reduction in haemoglobin levels that can lead to myocardial ischaemia. Hence, the Canadian drug authority has ruled that rosiglitazone should not be used in any of these situations: in patients taking insulin, in combination with Metformin and a sulphonylurea drug, or in patients diagnosed with any degree of heart failure, either past or current, even that which is very mild.
Strengthening the credibility of clinical research

The story of rosiglitazone is one of death, greed, and corruption, according to the Staff Report of the United States Senate Committee on Finance, released on Feb 20, 2010. The 2-year investigation by Senators Max Baucus, Chuck Grassley, and others, suggests that excess cardiovascular events in patients taking rosiglitazone appeared as early as 2004, but that the manufacturer, Glaxo SmithKline (GSK), intimidated researchers and manipulated the scientific process for commercial advantage. RECORD, one of the studies at the centre of this storm, was published by The Lancet in 2009. The Staff Report claims that GSK unblended the data 2 weeks before approaching the RECORD steering committee to suggest an interim analysis. GSK maintains that the company has been diligent in investigating rosiglitazone’s safety and points to the fact that the drug is still licensed by the US Food and Drug Administration. Add to this controversy Steven Nissen’s account, published on March 24 in the Journal of the American Medical Association, of a manuscript leaked by a peer-reviewer, indiscreet industry emails, and clandestine tape recordings, and one has the ingredients of a John Grisham novel.
Rosiglitazone, marketing, and medical science

Casually following the fortunes of the blockbuster diabetes drug rosiglitazone (Avandia), you can’t help but imagine a Hollywood thriller. There is the scene where a leading scientist secretly records a meeting with drug company executives, a high powered congressional investigation, and a bitter legal battle waiting in the wings. Yet when you look more closely, the facts are even stranger than fiction. An expensive new drug shown to raise the risk of heart failure and suspected of increasing the chance of heart attacks has been taken by millions of people around the world and is being kept on the market by an industry funded regulatory system, despite calls from senior safety experts to withdraw it. For its part, the drug’s manufacturer strongly denies the link with heart attacks and points to evidence to back its claims. But the details of this unfolding real life drama suggest a now familiar merging of medical science and drug marketing.

BMJ/10 APRIL 2010/VOLUME 340
SUMMARY AND COMMENT

More Bad News for Rosiglitazone

June 30, 2010/Frederick A. Masoudi. MD. MSPH

Mounting evidence of adverse cardiovascular effects continues to erode justification for its use.

Reviewing:  Graham DJ et al. JAMA 2010 Jun 28;
            Juurlink DN. JAMA 2010 Jun 28;
            Nissen SE and Wolski  K. Arch Intern Med 2010 Jun 28;
Pioglitazone: Risk of Congestive Heart Failure

The innovator of pioglitazone, Takeda Pharmaceuticals, has issued additional guidelines and warnings on the use of drug in Type II diabetes. Briefly it states that:

• Pioglitazone is not for all type 2 diabetics.

• It can cause fluid retention that can precipitate or worsen congestive heart failure (CHF). There is 39 percent increase in the risk of CHF in patients taking pioglitazone compared to those who are not on this medicine. It is not to be used in moderate to severe heart failure.

• LFTs must be done before starting pioglitazone and periodically thereafter. Patients must consult their doctors if there is rapid weight gain, shortness of breath, nausea, vomiting, abdominal pain, tiredness, loss of appetite, dark urine or yellowish of skin.
# The Story of Oral Hypoglycaemic Agents

<table>
<thead>
<tr>
<th>Insulin Secretagogue (sulfonylurea or shorter–acting meglitinide)</th>
<th>Metformin</th>
<th>α- Glucosidase Inhibitor</th>
<th>Thiazolidinedione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas contraindicated in severe liver/renal disease. Meglitinides useful for postprandial hyperglycemia or hypoglycemia with sulfonylureas Nateglinide safe with liver / renal disease. If obese, Renal/liver function normal No acute illness, GI disease, CHF, or alcohol abuse Cr &lt; 1.4 (women) Cr &lt; 1.5 (men) Hold if IV contrast dye procedure &gt;= 80 yr if renal function not reduced</td>
<td>Milder presentation If postprandial hyperglycemia is predominant pattern No GI disease</td>
<td>Abdominal obesity, additional signs of metabolic syndrome (insulin resistance, hypertension, and dyslipidemias) LFT, normal, monitor at baseline, every 2 mo for 1st yr, and periodically thereafter No hepatic impairment No NYHA Class III or IV CHF If edema, lower dose and/or add diuretic Safe with renal disease</td>
<td></td>
</tr>
</tbody>
</table>
Diabetes Drugs Don’t Boost Beta-Cell Function

“We did not find any evidence that either pioglitazone or metformin improved beta-cell function,” researchers conclude.


April 2007 DOCNEWS
UNIVERSITY GROUP DIABETES PROGRAMME (UGDP 1961 TO 1970)

This landmark multicentric clinical trail was designed elaborately by the high priests in academic institutions across the length and breadth of the USA and studied 823 diabetic patients for 9 years; the full report of the study was published in 1970\(^4\)

The salient points to note are:

a. Biguanide drug (Phenformin) was dropped from the trail during the 6\(^{th}\) year on account of significant increase in hypertension and cerebrovascular stoke observed in this treatment group.

b. Sulfonylurea (Tolbutamide) group was found to have more cardiovascular morbidity! mortality than the Insulin or placebo (no drug) group.

A hue and furore on the Pros and cons of the UGDP findings followed for the next one year with about 100 protagonists and over 150 antagonists publishing their findings. A consensus process followed and all diabetologists agreed that the trial was not fool proof and hence continued use of sulfonylurea drugs were thought to be safe provided they were used according to specified guidelines, following the failure of Diet and Exercise in controlling cases of NIDDM. (ADA Policy Paper, 1979)\(^5\).

This study of NIDDM (type 2 diabetes) with 23 centres recruiting 5102 patients with newly diagnosed type 2 DM involved different modalities of treatment with a follow-up period of nearly 14 years. The cost of the study, difficult to calculate, but conservatively estimated to be several billions of pounds. The findings revealed again what was well known from the times of Jean Pirat (over 30 years ago) that tight control of diabetes sharply reduces risk of blindness, kindly failure and more importantly heart disease; also tighter control of blood pressure along with diabetes reduced the risk of strokes, and other diabetes related deaths also by a third\(^8\).

The UKPDS also throws up important bomb-shells.

a. More patients treated with chlorpropamide developed high B.R and hence it was withdrawn from the study.

b. In a randomized sub study, the addition of Metformin to the existing sulfonylurea drug, and intention-to-treat analysis showed that the group assigned to combined Metformin / sulfonylurea therapy had a 96% increase in diabetes-related deaths and a 60% increase in all cause deaths compared with the patients assigned to continue maximal dose of sulfonylurea drugs alone\(^9\).

What is the outcome of these findings in clinical practice? There is a sharp resurgence and upward trend in the usage of Metformin and sulfonylurea / Metformin combinations in the world led by the USA! Truly the human brain and its behavior is the most baffling thing to fathom on this plant earth!!.
Shame: the elephant in the room
Managing shame is important for improving health care

Frank Davidoff – USA.

In 1960’s the results of UGDP showed that Tolbutamide, was associated with a significant increase in mortality in patients who developed Myocardial Infarction. The obvious response from Medical Profession should have been gratitude: here was an important way to improve the safety of Clinical Practice. But in fact the response was doubt, outrage, even legal proceedings against the investigators; the controversy went on for years. Why?
Diabetes Worldwide

Estimated number (in millions) of people with diabetes, worldwide:*

1985: 30 million
1995: 135 million
2003: 194 million
2025: 330 million

Increase in deaths from diabetes over next 10 years:†

<table>
<thead>
<tr>
<th>Region</th>
<th>Increase</th>
</tr>
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<tbody>
<tr>
<td>India</td>
<td>35%</td>
</tr>
<tr>
<td>the Americas</td>
<td>80%</td>
</tr>
<tr>
<td>the western Pacific and eastern Mediterranean regions</td>
<td>50%</td>
</tr>
<tr>
<td>Africa</td>
<td>&gt;40%</td>
</tr>
</tbody>
</table>

†Preventing Chronic Diseases: a vital investment, World Health Organization, 2005.

This issue of the Professional Section Quarterly was provided as a professional courtesy by Pfizer Inc.
POST PRANDIAL HYPERGLYCEMIA is associated with cardiovascular disease and mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Hoorn Study(^1)</td>
<td>2-h glucose better predictor of mortality than HbA(_1c)</td>
</tr>
<tr>
<td>Honolulu Heart Program(^2)</td>
<td>1-h glucose predicts coronary heart disease</td>
</tr>
<tr>
<td>Chicago Heart Study(^3)</td>
<td>2-h postchallenge glucose predicts all-cause mortality</td>
</tr>
<tr>
<td>DECODE(^4)</td>
<td>High 2-h postload blood glucose is associated with increased risk of death, independent of fasting glucose</td>
</tr>
<tr>
<td>Coutinho et al.(^5)</td>
<td>2-h glucose associated with CHD</td>
</tr>
<tr>
<td>Whitehall Study, Paris Prospective Study and Helsinki</td>
<td>2-h postchallenge glucose predicts all-cause and CHD mortality</td>
</tr>
<tr>
<td>Policemen Study(^6)</td>
<td></td>
</tr>
<tr>
<td>Diabetes Intervention Study(^7)</td>
<td>Postmeal but not fasting glucose is associated with CHD</td>
</tr>
</tbody>
</table>

Future of Health Care
(How to Restore Wholeness?)

Editors
Jacob Abraham, FAMS
Mathangi Ramakrishnan, FAMS
C.V. Krishnaswami, FAMS

Based on the Proceedings of the Public Symposium
Conducted by
The Tamilnadu Chapter of
National Academy of Sciences, Chennai, India
(March 2000)
Sponsored by
The National Academy of Medical Sciences, New Delhi
DIABETES IN THE THIRD MILLENNIUM – QUO VADIS DOMINI? Dr.C.V.Krishnaswami (2000)


During the past decade this mega clinical trial with multimega hype was presented to the medical fraternity, VIZ, the results of an exhaustively planned, meticulously implemented, superbly controlled and randomized clinical trial involving 23 centres and 1441 patients with IDDM, and costing over 120 million US$. The findings confirmed (what no sane-thinking diabetologist ever doubted) that “normalizing” blood sugars and HBA1C, throughout the trial period could reduce the micro vascular complications up to 50% or more and even reverse it to a lesser extent. But what was the price to pay?

a. Less than 10% of the participants achieved the target control!

b. 300% more incidence of severe, crippling hypoglycaemia\(^7\) and

c. The protocol used in achieving the near normalization’ of blood sugars and HBA1C in the DCCT trial was so impractical that, even 7 years after the acceptance of the findings of the study by diabetologists the world over, to say that Not even one Centre anywhere in the World implements this type of control in their IDDM patients is indeed the saddest commentary of the usefulness of this mega exercise. Nobody has discussed the why of this aspect in the follow-up. The report is evidently for the archives.
On February 6, 2008, the National Heart, Lung, and Blood Institute, which sponsors the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Trial, announced that it has stopped the intensive blood glucose control sub-study due to safety concerns. The trails randomized patients with diabetes and vascular disease and vascular disease or multiple cardiovascular risk factors to an intensive treatment program targeting normal blood glucose values and A1C less than 6% or a standard treatment program with an A1C between 7% and 7.9%. The intensive participants in ACCORD are now being switched to the standard treatment program because of increased death rate in the intensive treatment program (14 deaths per 1,000 patients per year versus 11 per 1,000 patients per year in the standard treatment program; a difference of 0.3 deaths per 100 patients per year)
Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomized trial

Interpretation

Microvascular benefits of intensive therapy should be weighed against the increase in total and cardiovascular disease-related mortality, increased weight gain, and high risk for severe hypoglycaemia.
Intensive glucose control in high-risk diabetes offers mixed results, according to two new analyses from the ACCORD trial.

In ACCORD, patients with type 2 diabetes and elevated cardiovascular risk were randomized to intensive glucose control or standard therapy. About half were also assigned to intensive or standard blood pressure control, and the other half to combination or standard lipid therapy. Intensive glucose control was stopped early, in 2008, because of increased mortality.

Now, writing in the Lancet, ACCORD researchers report that the glucose-control groups did not differ in composite outcomes measuring kidney function, diabetic eye complications, and peripheral neuropathy. However, several components of the composite outcomes (e.g., microalbuminuria, cataract extraction) were less common with intensive glucose control.

And in the New England Journal of Medicine, ACCORD researchers observe that both intensive glucose control and combination lipid therapy reduced progression of retinopathy, while intensive BP control did not.

Despite the microvascular benefits, the Lancet authors conclude, the increased mortality makes aggressive hemoglobin targets in high-risk diabetes seem “imprudent”.
In type 2 diabetes
Explore the possibilities
The first and only DPP-4 inhibitor

See the mechanism of action of JANUVIA »

Enhancing physiology
- Glucose-dependent mechanism targets 2 key defects: insulin release and hepatic glucose production

Enhancing control
- Powerful A1C reductions as monotherapy
*Dipeptidyl peptidase-4.

Important Information About JANUVIA

JANUVIA is indicated, as an adjunct to diet and exercise, as monotherapy to improve glycemic control in patients with type 2 diabetes mellitus.

JANUVIA is indicated to improve glycemic control, in combination with metformin or a thiazolidinedione (TZD), in patients with type 2 diabetes when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The recommended dose of JANUVIA is 100 mg once daily, with or without food, as monotherapy or as combination therapy with metformin or TZD as an adjunct to diet and exercise.

A dosage adjustment is recommended in patients with moderate or severe renal insufficiency or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis.

The use of JANUVIA in combination with medications known to cause hypoglycemia, such as sulfonylureas or insulin, has not been adequately studied. Research is ongoing.

The adverse reactions, regardless of investigator assessment of causality, in ≥5% of patients treated with JANUVIA and more commonly than in patients treated with placebo, were upper respiratory tract infection, nasopharyngitis, and headache.

No dosage adjustment is required based on age; however, because JANUVIA is substantially excreted by the kidney, it may be useful to assess renal function in elderly patients prior to initiation and periodically thereafter.

The incidence of selected gastrointestinal (GI) adverse reactions in patients treated with JANUVIA 100 mg vs placebo was as follows: abdominal pain (2.3%, 2.1%); nausea (1.4%, 0.6%); and diarrhea (3.0%, 2.3%).

†AINS HEALTH, NPA Plus™, October 2006-June 2007.
In placebo-controlled monotherapy studies of patients with type 2 diabetes, once-daily JANUVIA:

Powerful A1C Reductions

Primary analysis—24-week study

Total study population (N=473)
Mean baseline A1C 8%

<table>
<thead>
<tr>
<th>JANUVIA (n=229)</th>
<th>JANUVIA (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in A1C, %</td>
<td>Mean change in A1C, %</td>
</tr>
<tr>
<td>-0.8%</td>
<td>-0.4%</td>
</tr>
<tr>
<td>vs placebo (n=244) P&lt;0.001</td>
<td>vs placebo P&lt;0.001</td>
</tr>
</tbody>
</table>

Pooled analysis of 18- and 24-week studies—prespecified subgroup analysis at 18 weeks

- Mildly elevated A1C <8%, n=411: -0.6% reduction
- Moderately elevated A1C ≥8% to <9%, n=239: -0.7% reduction
- Highest elevated A1C ≥9%, n=119: -1.4% reduction

JANUVIA helps control glucose without weight gain or increased risk of hypoglycemia and with a low rate of GI disturbances

Monotherapy Efficacy of JANUVIA

A1C Reduction

Incidence of Side Effects

Study Designs

JANUVIA targets 2 key defects

Decreases glucagon release

Increases insulin synthesis and release

See the mechanism of action of JANUVIA
Body weight did not increase from baseline

<table>
<thead>
<tr>
<th>Change from baseline, kg</th>
<th>JANUVIA 100 mg (n=376)</th>
<th>Placebo (n=273)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.4</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

\[ P = 0.01 \]

Overall incidence of hypoglycemia was similar to placebo

<table>
<thead>
<tr>
<th>Overall incidence of hypoglycemia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>JANUVIA 100 mg (n=443)</td>
</tr>
<tr>
<td>Placebo (n=363)</td>
</tr>
<tr>
<td>1.1</td>
</tr>
<tr>
<td>0.6</td>
</tr>
</tbody>
</table>

\[ P = \text{NS} \]

Low rate of GI disturbances, %

<table>
<thead>
<tr>
<th>Selected GI adverse reactions</th>
<th>JANUVIA 100 mg (n=443)</th>
<th>Placebo (n=363)</th>
<th>[ P = \text{NS} ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>2.0</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1.6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.7</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.3</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

In controlled clinical studies as both monotherapy and combination therapy, the overall incidence of adverse reactions with JANUVIA was similar to that reported with placebo.

\*All Patients as Treated (APaT) population, excluding events after initiation of antihyperglycemic rescue therapy.

\*The safety and tolerability end points presented were prespecified for additional statistical assessment as part of the Phase III statistical analysis plan.

Important Information About JANUVIA

http://www.januvia.com/sitagliptin/januvia/hcp/efficacy/pooled_mono.jsp
Complementary effect without weight gain or increased risk of hypoglycemia and with a low rate of GI disturbances

More than twice as many patients uncontrolled on metformin got to

as many patients uncontrolled on pioglitazone got to ADA goal (A1C <7%) by adding JANUVIA (45% vs 23% for placebo)
JANUVIA is indicated to improve glycemic control, in combination with metformin or a thiazolidinedione (TZD), in patients with type 2 diabetes when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The recommended dose of JANUVIA is 100 mg once daily, with or without food, as monotherapy or as combination therapy with metformin or a TZD as an adjunct to diet and exercise.

A dosage adjustment is recommended in patients with moderate or severe renal insufficiency or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis.

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The incidence of selected gastrointestinal (GI) adverse reactions in patients treated with JANUVIA 100 mg vs placebo was as follows: abdominal pain (2.3%, 2.1%); nausea (1.4%, 0.6%); and diarrhea (3.0%, 2.3%).

JANUVIA is a trademark of Merck & Co., Inc. This site is intended only for healthcare professionals of the United States, its territories, and Puerto Rico. All rights reserved. 20652886(1)-04/07-JAN
In separate 24-week studies of patients with type 2 diabetes inadequately controlled on metformin or pioglitazone, once-daily JANUVIA:

**Add-on studies overview**

**Study: Add-on to metformin**

**Study: Add-on to pioglitazone**

**Once-daily JANUVIA:** More than twice as many patients uncontrolled on metformin got to ADA* goal by adding JANUVIA**¹¹**

**A similar decrease in body weight was observed for both treatment groups**⁵

<table>
<thead>
<tr>
<th>Change from baseline, kg</th>
<th>Metformin ≥1500 mg + JANUVIA 100 mg (n=399)</th>
<th>Metformin ≥1500 mg + placebo (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.7</td>
<td>-0.6</td>
</tr>
<tr>
<td>*P = NS</td>
<td></td>
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</table>

**Efficacy of JANUVIA in Combination therapy with metformin:**

- A1C Reduction
- Goal Achievement
- Incidence of Side Effects
- Study Design
In a 24-week study of patients with type 2 diabetes inadequately controlled on metformin greater than or equal to 1500 mg/day... Glycemic control by any measure...
Studies at ADA demonstrate vildagliptin improves islet health and glycemic control.

Vildagliptin, a novel investigational Incretin Enhancer, provides an effect equal to exendin-4, a recently approved injectable anti-diabetes drug, in improving measures of glycemic control and stimulating the growth of new insulin-producing beta cells in the islets of an animal model.

*Phase II study shows two key improvements: Greater beta cell function & improved insulin sensitivity*

*Preclinical findings show that vildagliptin provides effect equal to Byetta™*
Byetta (exenatide) injection

Indication.

BYETTA is an injectable prescription medicine that may improve blood sugar (glucose) control in adults with type 2 diabetes mellitus, when used with a diet and exercise program.

BYETTA is not insulin and should not be taken instead of insulin. BYETTA is not recommended to be taken with insulin. BYETTA is not for people with type 1 diabetes or people with diabetic ketoacidosis.
How Byetta works?

In people with type 2 diabetes, high blood sugar (glucose) is a big concern. After a meal, blood sugar levels rise, often too high. BYETTA slows down the rate at which glucose enters the bloodstream. BYETTA signals the pancreas to make the right amount of insulin at the right time to help blood sugar remain closer to normal.

After blood sugar levels off, BYETTA stops signaling the pancreas to produce insulin. This effect helps the body avoid low blood sugar, too (called hypoglycemia). As a result, BYETTA may help reduce your high blood sugar levels throughout the day. And that can mean better control, which can be one of the keys to helping manage your diabetes.

http://www.byetta.com
Important Safety Information for BYETTA® (exenatide) injection

Serious side effects can happen in people who take BYETTA, including inflammation of the pancreas, (pancreatitis) which may be severe and lead to death. Before taking BYETTA, tell your healthcare provider if you have had pancreatitis, stones in your gallbladder (gallstones), a history of alcoholism, or high blood triglyceride levels. Call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe, and will not go away. The pain may happen with or without vomiting and may be felt going from your abdomen through to your back.

Your risk for getting low blood sugar is higher if you take BYETTA with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of your sulfonylurea medicine may need to be lowered while you use BYETTA.

BYETTA should not be used in people who have severe kidney problems and should be used with caution in people who have had a kidney transplant. BYETTA may cause new or worse problems with kidney function, including kidney failure.

Before you use BYETTA, tell your healthcare provider if you have severe problems with your stomach, such as delayed emptying of your stomach (gastroparesis) or problems with digesting food.

Do not use BYETTA if you have had an allergic reaction to exenatide or any of the other ingredients in BYETTA. Severe allergic reactions can happen with BYETTA. Stop taking BYETTA and get medical help right away.

Tell your healthcare provider if you are pregnant or plan to become pregnant. It is not known if BYETTA will harm your unborn baby. Talk to your healthcare provider first if you are breastfeeding or plan to breastfeed.

The most common side effects with BYETTA include nausea, vomiting, diarrhea, dizziness, headache, feeling jittery, and acid stomach. Nausea most commonly happens when first starting BYETTA, but may become less over time.

These are not all the side effects with BYETTA. Talk to your healthcare provider about any side effect that bothers you or that does not go away.
Long – Acting Exenatide, Injected Once Weekly, Lowers HbA$_{1c}$ and Body weight.

The first incretin mimetic drug approved by the FDA.

**Comment:** A once-weekly injectable drug that lowers HbA$_{1c}$ levels and aids weight loss would be a welcome alternative to current insulin regimens. However, these researchers did not directly compare long-acting exenatide with insulin and did not provide long-term clinical outcomes.

-Bruce Soloway, MD  
*Published in Journal Watch General Medicine October 16, 2008*
FDA reports deaths with diabetes drug Byetta

WASHINGTON – Federal regulators are working on a stronger label for a widely used drug marketed by Amylin Pharmaceuticals Inc. and Eli Lilly & Co. after deaths were reported with the medication despite earlier government warnings.

More on Diabetes

4 More Deaths Reported Among Byetta Patients Health Day
Newer Blood Pressure Durg No Better Than Placebo in Preventing Stroke Health Day
From the publishers of The New England Journal of Medicine

FDA Updates Pancreatitis Warning on Diabetes Drug

The FDA is alerting physicians to six reports of hemorrhagic or necrotizing pancreatitis in patients using the diabetes drug exenatide (Byetta). Two of those patients diet.

In October 2007, the agency first warned physicians of a possible link between exenatide and acute pancreatitis, but there were no reports of hemorrhagic or necrotizing pancreatitis at that time.

The FDA says patients should not be given exenatide if pancreatitis is suspected. In addition. The drug should not be restarted after treatment for confirmed pancreatitis.
Information for Healthcare Professionals
Exenatide (marked as Byetta)

Update 8/18/2008: Since issuing Information for Healthcare Professionals in October 2007, FDA has received reports of 6 cases of hemorrhagic or necrotizing Pancreatitis in patients taking Byetta. Byetta is a medicine given by subcutaneous injection to help treat adults with type 2 diabetes. Of the 6 cases of hemorrhagic or necrotizing pancreatitis, all patients required hospitalization, two patients died and four patients were recovering at time of reporting. Byetta was discontinued in all 6 cases.

Byetta and other potentially suspect drugs should be promptly discontinued if pancreatitis is suspected. There are no signs or symptoms that distinguish acute hemorrhagic or necrotizing pancreatitis associated with Byetta from the less severe form of pancreatitis. If pancreatitis is confirmed, initiate appropriate treatment and carefully monitor the patient until recovery. Byetta should not be restarted. Consider antidiabetic therapies other than Byetta in patients with a history of pancreatitis.

FDA is working with the maker of Byetta, Amylin Pharmaceuticals, Inc., to add stronger and more prominent warnings in the product label about the risk of acute hemorrhagic or necrotizing pancreatitis.
## ANNUAL PHYSICAL AND ECONOMIC COST OF MEDICAL INTERVENTION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Deaths</th>
<th>Cost</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Drug Reactions</td>
<td>106,000</td>
<td>$12 billion</td>
<td>Lazarou(^1), Suh(^49)</td>
</tr>
<tr>
<td>Medical error</td>
<td>98,000</td>
<td>$2 billion</td>
<td>IOM(^6)</td>
</tr>
<tr>
<td>Bedsores</td>
<td>115,000</td>
<td>$55 billion</td>
<td>Xakellis(^7), Barczak(^8)</td>
</tr>
<tr>
<td>Infection</td>
<td>88,000</td>
<td>$5 billion</td>
<td>Weinstein(^9), MMWR(^10)</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>108,800</td>
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<td>Nurses Coalition(^11)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>199,000</td>
<td>$77 billion</td>
<td>Starfield(^12), Weingart(^112)</td>
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<tr>
<td>Unnecessary Procedures</td>
<td>37,136</td>
<td>$122 billion</td>
<td>HCUP(^3,13)</td>
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<tr>
<td>Surgery-Related</td>
<td>32,000</td>
<td>$9 billion</td>
<td>AHRQ(^85)</td>
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<tr>
<td><strong>TOTAL:</strong></td>
<td><strong>783,936</strong></td>
<td><strong>$282 billion</strong></td>
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Editorials represent the opinions of the authors and not necessarily those of the BMJ or BMA
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Self monitoring of blood glucose in type 2 diabetes
May not be clinically beneficial or cost effective and may reduce quality of life

RESEARCH, pp 1174, 1177

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Competing interests: None declared.
Provenance and peer review: Commissioned; not peer reviewed.

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doi: 10.1136/bmj.39538.469421.80
<table>
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<tr>
<th>STATINS</th>
<th>SUNLIGHT</th>
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<tr>
<td>SIMVA</td>
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<td>PRAVA</td>
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<td>ATORVA</td>
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<td>ROSUVA</td>
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<tr>
<td>S-FIBRATE (PPAR - AGENT)</td>
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<tr>
<td>S-EZETIMIBE</td>
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<tr>
<td>S-cachannel Blocker (AMLODIPINE)</td>
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<tr>
<td>S-ASPIRIN</td>
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</table>
Having low vitamin D levels has been linked with deaths from heart disease and other causes, adding to growing evidence about the "sunshine" vitamin's role in good health.

People with the lowest blood levels of vitamin D were about two times more likely to die from any cause during an eight-year period than those with the highest levels. The link with heart-related deaths was particularly strong in those with low vitamin D levels.

The study involved over 3,000 men and women in southwest Germany. Participants were aged 62 on average, and their vitamin D levels were checked in weekly blood tests.

It's estimated that at least 50 percent of older adults worldwide have low vitamin D levels, and a significant number of younger people may also be affected. Low vitamin D levels may result from spending less time outdoors, air pollution and a decline in your skin's ability to produce vitamin D from the sun as you age, the researchers said.

Sources:
This 86 year old lady a pavement dweller & destitute has never taken a Statin in her life!!!
Late Dr. Glen Gordon inventor EM Pulse Device & His wife Connie Gordon
Mechanism of EM Pulse & Pulsed Electro Magnetic Field Energy (PEMFE)

Prof. B.M. Hegde a renowned Cardiologist & former Vice Chancellor (Manipal University, India) who has introduced the use of EM Pulse in India, has opined that the concept of the Electro Magnetic Energy as a source to stimulate “built-in-healer” in the human body, would act by releasing endorphins and regulate hormones.

The three important tissue protein that are stimulated by pulse electro magnetic field energy (PEMFE) to reverse the condition of “deceased or dysfunction were the chaperony proteins” viz. the heat-shock protein 70, nitric oxide synthase and VEGF 165 gene protein.

They play a remarkable role in enhancing the natural healing process of human body tissues in any part of the body including heart, brain, bones, muscles and all other tissues, more than 1000 fold, helping to repair any deficit caused by in a dramatic fashion. However it should be noted that they do not act in dead cells or dead tissues. For further details of research in energy medicine particularly the PEMFE please refer to www.pubmedinfo.com.
<table>
<thead>
<tr>
<th>Name</th>
<th>Mr.VR</th>
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<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
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<tr>
<td>Age</td>
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Before Treatment
After Treatment
Thank You All