

**PRACTICAL POINTERS**  
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**MARCH 2011**

**DIABETES, FASTING BLOOD GLUCOSE AND RISK OF CAUSE-SPECIFIC DISEASE [3-1]**

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**26<sup>th</sup> YEAR OF PUBLICATION**

This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS SECTION**

**HIGHLIGHTS** condenses the contents of studies, and allows a quick review of pertinent points of each article.

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*EDITORIAL COMMENTS are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at [www.practicalpointers.org](http://www.practicalpointers.org)

Richard T. James Jr. M.D.

Editor/Publisher.

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## HIGHLIGHTS AND *EDITORIAL COMMENTS* MARCH 2011

*A 50 Year Old With Diabetes Is About 6 Years Younger At The Time Of Death Than A Counterpart Without Diabetes.*

### 3-1 DIABETES MELLITUS, FASTING GLUCOSE, AND RISK OF CAUSE-SPECIFIC DISEASE

The presence of diabetes doubles risk of a wide range of cardiovascular diseases. Diabetes is also associated with non-vascular disease.

This study aimed to provide a reliable estimate of independent associations of baseline diabetes and fasting blood glucose (**FBG**) levels with risk of cause-specific death.

The Emergent Risk Factors Collaboration analyzed data from 820 900 individuals--a total of over 2 million person-years. The analysis focused on individual participant data from 97 prospective studies with information about the diagnosis of diabetes, and with information about FBG levels at baseline.

All studies included records of cause-specific deaths in participants who had accrued more than one year of follow-up. No participant had known previous vascular disease at baseline.

Assessed whether diabetes status and baseline FBG levels related to death from any cause, and main components including death from cancers, vascular diseases, and non-vascular conditions.

Calculated hazard ratios (**HR**; diabetes vs no-diabetes), pooled across studies.

Estimated cumulative survival from age 35 and older in those with and those without diabetes at baseline.

Among the 820 900 participants, the mean age was 55; 52% male; 40 116 (6%) had diabetes at baseline. During 12.3 million person-years of follow-up, the median time to death was 13.6 years.

Hazard ratios for death after adjustment: <sup>b</sup>

	Diabetes vs no diabetes
All deaths	1.8
Cancer	1.25
Vascular	2.3
Non-vascular-	
Non-cancer <sup>c</sup>	1.83

(b. Adjustment at baseline for age, sex, smoking and BMI)

(c Deaths from renal disease, liver disease, pneumonia, other infectious diseases, mental

disease, non-hepatic digestive diseases, external causes, intentional self-harm, nervous system disease, and COPD)

Fasting blood glucose and mortality: Levels exceeding 100 mg/dL, but not levels of 70-100 were associated with excess risk of death. As levels rose above 100, HRs for every 18 mg/dL rise, deaths increased by 1.05 for deaths from cancer, 1.13 for vascular, 1.10 for non-vascular, and 1.10 for any cause.

HRs for various FBG after excluding those with known history of diabetes (ie, self-reported) at baseline. As compared with FBG 70 to 100,

FBG 126 or more <sup>d</sup>	HR for death diabetes vs no diabetes
Cancer deaths	1.39
Vascular	1.89
Non-vascular; non-cancer	1.54

(d There was no formal (self-reported) diagnosis of diabetes, perhaps because the standards were not established at the time of the studies, or because the diagnosis was not made. Ed.)

FBG 100 to 125	HR for death
Cancer deaths	1.13
Vascular deaths	1.17
Non- cancer; non-vascular	1.17
Diabetes at baseline	
FBG less than 126	1.50
FBG 126 or more	2.16

In addition to the excess risk of vascular disease, diabetes is associated with substantial premature mortality from several cancers, infectious disease, external causes, intentional self-harm, and degenerative diseases, independent of several major risk factors.

On average, a 50 year old with diabetes, but with no history of vascular disease, is about 6 years younger at the time of death than a counterpart without diabetes.

The study did not observe appreciable alteration in the associations between diabetes and mortality after adjustment for several other risk factors (systolic BP, adiposity, inflammation biomarker, insulin, or renal function).

Conclusion: In addition to vascular disease, diabetes is associated with substantial premature death from several cancers, infectious disease, external causes, increased self-harm and degenerative disorders, independent of several major risk factors.

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*This massive and important study received input from experts in England, Scotland, USA, Sweden, Norway, and Iceland. It is all the more important for primary care because diabetes is largely a preventable disease.*

*Few patients' with diabetes realize the dangers of their disease. The authors state that death rates from diabetes are about equal to those of smoking.*

*I was not aware of the adverse effect of increased FBG, even at relatively low levels.*

### ***“Significant Benefits from Antihypertensive Treatment”***

## **3-2 ANTIHYPERTENSIVE TREATMENT AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE EVENTS AMONG PERSONS WITHOUT HYPERTENSION: A Meta-analysis**

Prospective studies have established a strong, graded, and independent positive association between BP levels and risk of CVD, stroke, and premature death. Increased risk of CVD begins at systolic as low as 115. Many strokes and CVD events occur in patients with systolic BP less than 140.

More than 30% of the general population has prehypertension. (BP 130-139/86-89)

In persons with prehypertension, about 90% have at least one risk factor for heart disease or stroke.

Clinical trials have documented that lowering BP reduces CVD mortality among patients with hypertension. Several randomized trials of lowering BP for prevention of CVD have demonstrated benefit among persons with prehypertension, and even in those with normal BP. Others have shown no benefit.

This meta-analysis evaluated the association between antihypertensive treatment and secondary prevention of CVD events and all-cause mortality among persons without clinically defined hypertension (lower than 140/90).

Extensive search discovered 874 possibly relevant randomized-controlled trials. Of these, 25 were included in the meta-analysis. All were limited to individuals over age 19. Antihypertension treatment, entry criteria, and duration varied between trials. Mean age varied between 55 and 68; 75% were male.

All subjects had a history of CVD: clinical evidence of recent myocardial infarction (**MI**), congestive heart failure, coronary artery disease, stroke, or the CVD equivalent--type-2 diabetes. (To classify the study as secondary prevention.)

The 25 studies incorporated data from 64 162 participants, all had a baseline BP under 140/90.

Pooled overall relative risks (**RR**) and absolute risk reduction: (Treatment vs placebo)

	RR	Absolute risk reduction per 1000
Stroke	0.77	-7.2
MI (fatal and non-fatal)	0.80	-13.3
Congestive heart failure	0.71	-43.6
Composite CVD outcomes	0.85	-27.1
CVD mortality	0.83	-15.4
All-cause mortality	0.87	-13.7

The overall pooled results from antihypertensive treatment, compared with control, showed a significant reduction in risk for stroke, CHF events, CVD events, and all-cause mortality.

Conclusion: Prehypertension affects nearly 1/3 of the adult population, and carries an elevated risk for CVD incidence and mortality. Among patients with a clinical history of CVD, but without hypertension, antihypertensive treatment was associated with decreased risk of stroke, CHF, CVD events, and all-cause mortality. We do not know if benefits occur in patients without CVD.

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*So, what is "hypertension"?*

*What is prehypertension? <sup>1</sup>*

*What is normal? (Normal systolic then could be 115 to 129; or 115 to 119)*

*Do we really have good definitions? Presently they are defined by arbitrary cutpoints. If prehypertension is 120-130, and hypertension begins at 140, normal must be narrowly defined as 115-119.*

*I believe hypertension may be defined as the BP level, which in an individual causes organ damage, or is associated with increased risk of organ damage.*

*The likelihood of organ damage determines the benefit / harm-cost ratio of drug therapy. An assessment of the benefit / harm-cost ratio is essential for every patient.*

*When systolic is below 140, I doubt BP is the predominant risk factor.*

*All risk factors must be treated. Lifestyle intervention is the predominate therapy, especially in younger patients. Prescribing drugs to younger patients would expose them to adverse effects and costs of drugs over a longer time. Older patients are more at risk for CVD events. For them, drug therapy would be more beneficial, and would be taken for a shorter time.*

*This study assessed treatment of prehypertension in patients who had established CVD. What about patients who have a long list of risk factors and have no history of CVD events? Certainly, they are at*

*increased risk compared with those who have few risk factors. Would preventive measures be termed primary prevention or secondary prevention? How about tertiary prevention?*

*Prehypertension and hypertension (plus other risk factors) in our population are so common as to be almost universal. This raises the issue of universal treatment with a “polypill”.*

**1** *The article defines systolic for prehypertension as 130-139; the editorial as 120-139 JNC VI defined prehypertension systolic as 130-139. JNC VII as 120-139. (Personal communication with Lydia A L Bazzano, MD, PHD, Tulane University)*

### **3-3 THE EFFECTS ON SURROGATES OF MAKING TREATMENT DECISIONS FOR OTHERS; Systematic Review**

Many adult patients near the end of life cannot make their own treatment decisions. Standard practice relies on surrogates to make decisions for them, typically in consultation with the patient’s physician.

If making treatment decisions has a negative psychological effect, it might impair a surrogate’s ability to protect patients who lack decision-making capacity, and would represent a harm to surrogates. In addition, it might conflict with the preferences of patients who do not want to be a burden to their family.

This review assessed the effects on surrogates of making treatment decisions for adults who cannot make their own decisions.

Literature search identified 5221 possibly relevant studies. Of these, 40 met inclusion criteria. Of these 40 studies (n = 2854 surrogates), 29 used qualitative data and 11 used quantitative data. More than half of the surrogates were family members of the patients. Most were surveyed months to years after making the treatment decisions, the majority of which were end-of-life decisions (choosing to initiate, withhold, continue, or withdraw life-sustaining treatment).

The most common reported stressors::

- Unsure of the patient’s wishes
- Uncertain prognosis
- Discomfort with the hospital environment
- Poor communication with the clinician
- Insufficient time
- Sense of sole responsibility
- Uncertainty or guilt over decisions

Making treatment decisions for incapacitated loved ones places an emotional burden on at least one third of surrogates.

Being confident of which treatment the patient would want has an important protective effect for surrogates.

Methods for making treatment decisions would ideally promote at least 3 goals:

- 1) Identifying treatments that are consistent with the patient's preferences.
- 2) Respecting patient's preferences regarding how treatment decisions are made.
- 3) Protecting the patient's family and loved ones.

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*This is an important aspect of primary care medicine. Read the full abstract.*

*Primary care clinicians should encourage elderly patients to think about advanced directives, living wills, and a durable power of attorney. It is important to get the whole family on the same page. The elderly patient should leave no uncertainty. Nothing splits a family more than disagreement about terminal care. Instructions should not only be in writing, but also freely discussed when families get together for holidays.*

*I believe that many elderly persons are now considering death a normal and necessary part of living, not a reason for dread. They seek a "good death". They realize that some states of incapacity are worse than death.*

*If I remember accurately, one proposed change in the new health care law allowed payment to primary care clinicians for counseling elders and families about the importance of planning for terminal care. Some detractors termed the effort "Pulling the plug on Grandma".*

### **3-4 EFFICACY OF DRUG TREATMENT FOR GENERALIZED ANXIETY DISORDER: Systematic Review and Meta-analysis**

Generalized anxiety disorder (**GAD**) is a chronic or relapsing condition characterized by persistent and pervasive worrying and tension, which causes substantial personal distress and imposes a considerable economic burden.

Anxiety disorders are among the most prevalent of mental disorders and GAD is the most common and most impairing anxiety disorder in primary care. The degree of disability attributed to GAD compares with that of major depression and is similar to that of chronic physical illnesses such as arthritis and diabetes.

This systematic review included only double blind, placebo- controlled randomized trials of any

duration; and published systematic reviews and meta-analyses of randomized-controlled trials in adults receiving any drug for treatment of GAD. (1980-2009)

Data consisted of treatments and dosage, methods for diagnosis of GADS, duration, and relevant outcomes (anxiety scores at baseline and end of study, and proportion of responders and remitters).

The extracted data were combined in a series of mixed treatment meta-analyses, which incorporated evidence from trials, indirectly comparing drugs with a common comparator (such as placebo) as well as evidence from head-to-head trials. Application of this approach within a Bayesian framework enables treatments to be ranked in terms of the probability of each treatment being the first or most effective for each outcome measure.

Primary outcome measures:

- 1) Response: The proportion of patients who experienced at least a 50% reduction from the baseline score on the Hamilton anxiety scale. (*Available on Google Ed.*)
- 2) Remission: The proportion of patients with a final score 7 or less. (Of 56)
- 3) Tolerability: Withdrawals because of adverse events.

Data from the 27 publications allowed analyses to be performed for 9 treatments: duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine, and venlafaxine. <sup>1</sup>

Probabilistic analysis of drugs by outcome measures.

(Figures in parentheses indicate percentage chance of being ranked first)

Rank	Response	Remission	Tolerability
1	Fluoxetine (63)	Fluoxetine (61)	Sertraline (49%)
2	Lorazepam (17)	Escitalopram (26)	Pregabalin (7%)*
3	Duloxetine (3)	Vnlafaxine (4)	Fluoxetine (38%)

4 - 9 All other drugs had a percentage probability of being first of 7% or less.

(\*I do not understand this rating )

Fluoxetine was rated first in terms of response and remission. Sertraline was first for tolerability. (Ie, had lowest probability of withdrawals.)

All active treatments were favored over placebo. Placebo was favored over all treatments in terms of withdrawal.

Conclusion: In this study, fluoxetine was most effective in terms of response and remission, and sertraline was first in terms of tolerability.

<sup>1</sup> Escitalopram [*Lexapro*]; fluoxetine [*Prozac*]; paroxetine [*Paxil*]; sertraline [*Zoloft*]; and venlafaxine [*Effexor*] are selective serotonin reuptake inhibitors. (SSRI) Duloxetine [*Cymbalta*] is a serotonin, norepinephrine

reuptake inhibitor. Pregabalin [*Lyrica*] and tiagabine [*Gabitrile*] are antoconvulsants. Lorazepam [*Ativan*] is a benzodiazepine.

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*This is certainly not a definitive study. Placing fluoxetine [*Prozac*] and sertraline [*Zoloft*] first is tentative. Duration of the trial was short. This leaves the primary care clinician room to choose. I would choose the drug with which I was most familiar. If there were no choice, I would begin with Prozac at low dosage, then, if necessary, proceed with higher doses or switch to another drug. Fluoxetine has the advantage of being available at some pharmacies for \$4.00 for a month's supply.*

*Drug therapy is not alone in treating GAD. A patient ear of the primary care clinician may help.*

*The Hamilton Anxiety Rating Scale contains 14 questions related to anxiety, each having 0 to 4 responses, depending on severity of the symptom. (Total number of responses = 70, including zeros indicating the symptom is not present, to 4 indicating "very severe".) One questions asks specifically about depressed mood. Seven questions relate to somatic symptoms. I believe they may indicate some depression as well as anxiety.*

*I abstracted the article in detail because it is the first example of mixed treatment meta-analysis I have encountered. I still do not fully understand it, but with time, I believe I will. I expect to see similar studies in the future.*

### **3-5 GLUCAGON-LIKE PEPTIDE-1 ANALOGUES FOR TYPE 2 DIABETES: A Review Article**

Glucagon-like peptide-1 (**GLP-1**) is a naturally occurring peptide hormone released from the gut after eating.

GLP-1 has several important functions: 1) stimulates insulin secretion; 2) suppresses glucagon release (thereby reducing hepatic gluconeogenesis); 3) delays gastric emptying and promotes satiety.

It has a short half life (minutes) as a result of rapid breakdown by endopeptidases.

Two GLP-1 analogues (also known as incretin mimetics) are available for treatment of type-2 diabetes (**DM-2**) : exenatide and liraglutide. These are modified GLP-1 peptides which resist downgrading by endopeptidases. Their half-life is extended.

They are indicated as adjuncts to other treatments for DM-2.

The abstract discusses in more detail:

Properties of

Exenatide (*Byetta*)

Liraglutide (*Victoza*)

Safety issues  
Precautions  
Drug administration  
The future  
Costs

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*Practical Pointers has discussed GLP-1 analogues several times. They are an entirely new approach to treatment. Advantages include weight loss and low risk of hypoglycemia. If the costs come down and as long-acting preparations become more available, I believe they show great promise in treatment of DM-2.*

*Please read the full abstract for details. It condenses clinical information into a few pages.*

### ***The Evidence For Cancer Prevention Is Inconsistent And Inconclusive.***

#### **3-6 VITAMIN D AND PREVENTION OF CANCER-- Ready for Prime Time?**

The Institute of Medicine (IOM) is charged with determining the population needs for vitamin D (D) in North America. In 2011 a committee of the IOM published an updated Dietary Reference Intake for Vitamin D after reviewing the evidence linking D with skeletal and non--skeletal health outcomes.

The IOM concluded that D plays an important role in bone health and that the evidence provides a sound basis for determining the population's needs for it.

Based on D's importance to bone health, the recommended daily allowances (RDA) are 600 IU for persons age 1 to 70, and 800 IU per day for those over 70. This corresponds to a serum level of 25OHD of at least 20 ng/mL.

Because of the wide variation in sun exposure and skin synthesis of D, and the known risks of skin cancer, the recommendation was made under the assumption that skin exposure would be minimal.

The IOM also concluded that the prevalence of D inadequacy in North America has been overstated. Most North Americans have serum levels above 20, which is adequate for bone health in at least 95% of the population.

Four outcomes beyond bone health (cancer, cardiovascular, diabetes, and autoimmune disorders) were also considered. The IOM found that the evidence of them was inconsistent and inconclusive.

The committee's comprehensive review of the evidence of D's role in preventing cancer concluded that the research is inconsistent and does not establish a cause-effect relationship. Other recent reviews have reached similar conclusions. No large scale randomized controlled trial has been completed regarding the effect of D on cancer as the primary prespecified outcome. Most evidence thus far is

derived from laboratory studies, ecological correlations, and observational investigations of 25OHD levels. in association with cancer outcomes. Association studies have important limitations. Low 25OHD levels are also linked with confounding factors related to high cancer risk: Obesity (D becomes sequestered in adipose tissue), lack of physical activity (correlated with less time outdoors and less solar exposure), dark skin pigmentation (less synthesis of D), and diet or supplementation practices. Reverse causation biases may also occur if poor health reduces participation in outdoor activities and limited sun exposure lowers D levels.

Association cannot prove causation.

Many micronutrients that seemed promising in observational studies were not found to reduce cancer risk in randomized trials. (Eg, beta carotene, vitamins C and E, and folic acid.) Some were found to cause harm at high doses.

The theory that D can help prevent cancer is biologically plausible. Studies in cell culture and experimental models suggest that calcitriol promotes cell differentiation, inhibits cancer cell proliferation, and exhibits anti-inflammatory and anti-angiogenic properties. This suggests, but does not prove a role for D in cancer prevention.

Randomized trials are sparse. Three randomized trials have assessed the occurrence of cancer mortality as secondary outcomes. Results were null.

- 1) Oxford's UK: Of 2686 men and women given D or placebo. More cancers occurred in the D group. (188 vs 173; RR = 1.08)
- 2) Nebraska USA : Of 1179 postmenopausal women, those given D were less likely to develop cancer (13 vs 17; RR = 0.74)
- 3) Woman's Health Initiative USA: Of 32 282, subjects, those receiving D were less likely to develop cancer. (1634 vs 1655; RR = 0.98)

None was statistically significant.

Breast cancer: Three observational studies were inconclusive. The large Women's Health Initiative, which assessed breast cancer as a separate secondary outcome, found the D had no significant effect.

Colorectal cancer: Observational studies generally support an inverse relationship. In a meta-analysis of 5 prospective studies, subjects with a 25OHD level of 33 ng/mL had about half the risk of colorectal cancer as those with levels of 12 ng/mL. The European Prospective Investigation into Cancer and Nutrition found a similar strong inverse relationship. A study from Japan reported benefit only for rectal cancers. A British trial of D vs placebo and the Women's Health Initiative trial reported no benefit.

Prostate cancer: Eight of 12 nested case-control studies showed no association between baseline levels of 25OHD levels and risk.

Less common cancers: The large Colon Cancer Consortium Vitamin D Pooling Project of Rarer Cancers showed no evidence linking higher 25OHD levels with reduced risk of many cancers (endometrial, esophageal, gastric, pancreatic, kidney, ovary, and non-Hodgkin's lymphoma). Moreover the study reported an increased incidence of pancreatic cancer with 24OHD levels over 39 ng/mL. An increased incidence of esophageal cancer was also reported.

Despite biologic plausibility and widespread enthusiasm, the IOM found the evidence that D reduces cancer incidence and mortality of cancers was inconsistent and inconclusive.

NEJM April 14, 2011; 364: 1385-87 "Perspective", Editorial, first author JoAnn E Manson, Brigham and Women's Hospital, Harvard Medical School, Boston Mass. Dr. Manson is a member of the IOM Committee.

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*Recently, Practical Pointers has abstracted many articles about D --most suggesting a benefit. I hope this is the last until a large definitive randomized trial is published.*

*Is D going the way of "estrogens forever" and antioxidants?*

*In the past, many observational studies have overemphasized benefits of treatments. These are not fraudulent. It is the nature of observational studies, perhaps augmented by enthusiastic proponents of a new theory.*

*Meanwhile, what should the primary care clinician do about D? I believe many individuals in the US are deficient. Older patients who are house-confined or in nursing homes are not exposed to sunlight. Their diets may be deficient in D. Growing children may not get enough D and calcium.*

*The benefit / harm-cost ratio of D remains high, Benefits may be substantial; harms and costs are nil.*

*Fortunately, in medicine the truth will out. It may take years or decades.*

*I hope D will survive.*

## ABSTRACTS MARCH 2011

*A 50 Year Old With Diabetes Loses About 6 Years Of Life Counterpart With Those Without Diabetes.*

### 3-1 DIABETES MELLITUS, FASTING GLUCOSE, AND RISK OF CAUSE-SPECIFIC DISEASE

The presence of diabetes doubles risk of a wide range of cardiovascular diseases. Diabetes is also associated with non-vascular disease. We do not know whether such associations are direct (due to hyperglycemia) or indirect (due to underlying biological factors such as insulin resistance and hyperinsulinemia), or due to shared risk factors (obesity) or a combination.

Since diabetes is a multisystem disease, there is need for assessment of associations of diabetes with death from a broad range of diseases.

This study aimed to provide reliable estimates of independent associations of baseline diabetes and fasting blood glucose (**FBG**) levels with risk of cause-specific death.

#### STUDY

1. The Emergent Risk Factors Collaboration analyzed data from 820 900 individuals--a total of over 2 million person-years.
2. The analysis focused on individual participant data from 97 prospective studies with information about the diagnosis of diabetes, and with information about FBG levels at baseline.
3. All studies included records of cause-specific deaths in participants who had accrued more than one year of follow-up.
4. No participant had known previous vascular disease at baseline. Companion information was available for all about age, sex, smoking status, BMI, FBG and history of diabetes and subsequent cause-specific causes of death during follow-up.
- 5.. Information about type of diabetes (type 1 or type 2) was generally not available. The ages of participants suggested that the large majority was type 2.
6. Assessed whether diabetes status and baseline FBG levels related to death from any cause, and main components including death from cancers, vascular diseases, and non-vascular conditions.
7. Calculated hazard ratios (**HR**; diabetes vs no-diabetes), pooled across studies.
8. Estimated cumulative survival from age 35 and older in those with and those without diabetes at baseline.

## RESULTS

1. Among the 820 900 participants, the mean age was 55; 52% male; 40 116 (6%) had diabetes at baseline. During 12.3 million person-years of follow-up, the median time to death was 13.6 years. 123 205 deaths were recorded:

Cancer deaths	41 320
Vascular disease	44 407
Other causes	27 661
Unknown	9817

2. Diabetes and mortality:

- A. Crude overall rates of death were higher among participants with diabetes.

Deaths per 1000 person-years:

	Diabetes	No diabetes	HR (diabetes vs no diabetes)
All deaths	52	19	2.7
Cancer-specific death <sup>a</sup>	11	7	1.5
Vascular deaths	24	7	3.4

(The article states separate death rates for men and for women. I have averaged them for simplicity. Ed.)

(a Cancers of liver, pancreas, ovary, colorectum, lung, bladder, and breast.)

- B. Hazard ratios (diabetes vs no diabetes) for death after adjustment<sup>b</sup>

	Diabetes vs no diabetes
All deaths	1.8
Cancer	1.25
Vascular	2.3
Non-vascular-	
Non-cancer <sup>c</sup>	1.83

(b. Adjustment at baseline for age, sex, smoking and BMI)

(c Deaths from renal disease, liver disease, pneumonia, other infectious diseases, mental disease, non-hepatic digestive diseases, external causes, intentional self-harm, nervous system disease, and COPD)

3. Fasting blood glucose and mortality:

- A. Levels exceeding 100 mg/dL, but not levels of 70-100 were associated with excess risk of

death. As levels rose above 100, HRs for every 18 mg/dL rise, deaths increased by 1.05 for deaths from cancer, 1.13 for vascular, 1.10 for non-vascular, and 1.10 for any cause.

B. HRs for various FBG after excluding those with known history of diabetes (ie, self-reported) at baseline. As compared with FBG 70 to 100, HRs for death:

FBG 126 or more <sup>d</sup>	HR for death
Cancer deaths	1.39
Vascular	1.89
Non-vascular; non-cancer	1.54

(d There was no formal (self-reported) diagnosis of diabetes, perhaps because the standards were not established at the time of the studies, or the diagnosis was never made. .)

FBG 100 to 125	HR for death
Cancer deaths	1.13
Vascular deaths	1.17
Non- cancer; non-vascular	1.17
Diabetes at baseline	
FBG less than 126	1.50
FBG 126 or more	2.16
FBG lower than 70:	
Cancer	1.01
Vascular	1.32
Non vascular; non cancer	1.05

## DISCUSSION

1. In addition to the excess risk of vascular disease, diabetes is associated with substantial premature mortality from several cancers, infectious disease, external causes, intentional self-harm, and degenerative disease, independent of several major risk factors.
2. On average, a 50 year old with diabetes, but with no history of vascular disease, is about 6 years younger at the time of death than a counterpart without diabetes.
- 3, For comparison, the reduction in life expectancy is about 7 years for smokers.
- 4, About 40% of years of life lost from diabetes can be attributed to non-vascular causes, including 10% attributable to cancer.

5. There are also generally continuous associations with death between fasting blood glucose levels greater than 100 mg/dL. Hyperinsulinemia (or some closely related factor) may be directly related.
6. The study did not observe appreciable alteration in the associations between diabetes and mortality after adjustment for several other risk factors (systolic BP, adiposity, inflammation biomarker, insulin, or renal function).
7. The evidence for the association of diabetes with many cancers is marginally significant, and should be evaluated further.
8. Aside from cancers the study found associations of diabetes with renal and digestive disease and infectious disease. These results may reflect associated nephropathy, fatty liver disease, and suppression of cellular immunity.
9. The association with the substantial excess of deaths due to self-harm suggests an association with depression.
10. Patients with diabetes may consider cancer screening appropriate for their age and sex.
11. We do not understand the reason for the association between very low FBG and vascular death in persons without diabetes.
12. Collectively, the study broadens and intensifies the need for efforts to prevent and understand diabetes.

## CONCLUSION

In addition to vascular disease, diabetes is associated with substantial premature death from several cancers, infectious disease, external causes, increased self-harm, and degenerative disorders, independent of several major risk factors.

NEJM March 3, 2011;364: 829-41 Original investigation by the Emerging Risk Factors Collaboration

The ERFC is located at Cambridge University, Cambridge, UK

Supported by the British Heart Association, The U.K. Medical Research Council. Pfizer and others.

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***“Significant Benefits from Antihypertensive Treatment”***

**3-2 ANTIHYPERTENSIVE TREATMENT AND SECONDARY PREVENTION OF  
CARDIOVASCULAR DISEASE EVENTS AMONG PERSONS WITHOUT HYPERTENSION:  
A Meta-analysis**

Prospective studies have established a strong, graded, and independent positive association between BP levels and risk of cardiovascular disease (CVD), stroke, and premature death. Increased risk of CVD begins at systolic as low as 115. Many strokes and CVD events occur in patients with systolic BP less than 140.

More than 30% of the general population has prehypertension. (BP 130-139/86-89)

In persons with prehypertension, about 90% have at least one risk factor above optimal for heart disease or stroke, and at least one clinically high-risk factor for heart disease or stroke.

Among adults 35 years old or older, 17% with normal BP (129/85 or less), and 37% of those with prehypertension, progress to overt hypertension within 4 years unless they change lifestyles or use drug interventions. In adults over age 55, lifetime risks of developing hypertension is greater than 90%.

Clinical trials have documented that lowering BP reduces CVD mortality among patients with hypertension. Several randomized trials of lowering BP for prevention of CVD have demonstrated benefit among persons with prehypertension, and even in those with normal BP. Others have shown no benefit.

This meta-analysis evaluated the association between antihypertensive treatment and secondary prevention of CVD events and all-cause mortality among persons without clinically defined hypertension (lower than 140/90).

## STUDY

1. Extensive search discovered 874 possibly relevant randomized-controlled trials. Of these, 25 were included in the meta-analysis. All were limited to individuals over age 19. Antihypertension treatment, entry criteria, and duration varied between trials. Mean age varied between 55 and 68; 75% were male.
2. All subjects had a history of CVD: clinical evidence of recent myocardial infarction (MI), congestive heart failure, coronary artery disease, stroke, or the CVD equivalent--type-2 diabetes. (To classify the study as secondary prevention.)
3. The 25 studies incorporated data from 64 162 participants. All had a baseline BP under 140/90.

## RESULTS

1. Pooled overall relative risks (RR) and absolute risk reduction: (Treatment vs placebo)

	RR	Absolute risk reduction per 1000
Stroke	0.77	-7.2
MI (fatal and non-fatal)	0.80	-13.3

Congestive heart failure	0.71	-43.6
Composite CVD outcomes	0.85	-27.1
CVD mortality	0.83	-15.4
All-cause mortality	0.87	-13.7

2. The overall pooled results from antihypertensive treatment compared with control, showed a significant reduction in risk for stroke, CHF events, CVD events, and all-cause mortality.

## DISCUSSION

1. The meta-analysis is unique in that it is the first to focus on the association of antihypertensive medication used for secondary prevention of CVD events and all-cause mortality among patients without clinically defined hypertension.
2. Patients with a history of CVD, but with BP in the normal and pre-hypertensive range can obtain significant benefits from anti hypertensive treatment. (*There was no mention of treatment for other risk factors. Ed*)
3. Risk for CVD increases monotonically at all BP levels in the normal and prehypertensive range.
4. Although prehypertension affects nearly 70 million people in the US, and is associated with increased risk of CVD similar to that seen with hypertension, the use of antihypertensive treatment among persons with less than 140/90 has been debated.
5. According to the current algorithm for treatment of hypertension in persons with compelling indications (CHF, post-MI, high coronary disease risk, and recurrent stroke prevention) pharmacological treatment is indicated for those whose BP is not controlled below 140/90 with lifestyle interventions alone. Hypertension precedes development of CHF in the majority of patients and increases risk of MI and CHF.
6. Although pharmacological treatment for all individuals in this population is not economically feasible, a more reasonable strategy might be to identify groups within the prehypertension population who would obtain the greatest benefit from early pharmacological intervention.
7. For patients with diabetes, the current algorithm for treatment of hypertension indicates pharmacological treatment for those whose BP is not controlled to less than 130/80 with lifestyle interventions alone. However, the recent ACCORD BP trial, conducted in patients with diabetes, demonstrated no reduction in the rate of CVD event when systolic BP was controlled to less than 120, compared with less than 140.
8. In patients with BP less than 140/90, only 2 trials of antihypertensive treatment were conducted

in patients who were without a history of CVD or diabetes. They indicated benefit, but the studies were small and had relatively few events. We do not know if lowering BP in this group is beneficial. We do not know if treatment of prehypertension will benefit patients with specific risk factors such as elevated lipids, smoking, or chronic kidney disease.

9. Although antihypertensive drugs (ACE inhibitors, calcium blockers, angiotensin II blockers, beta-blockers, and diuretics) are generally well tolerated, they do have serious adverse effects.
10. We do not know the baseline BP level at which antihypertensive treatment should begin in patients with CVD or CVD equivalents such as diabetes.

## CONCLUSION

Prehypertension affects nearly 1/3 of the adult population, and carries an elevated risk for CVD incidence and mortality.

Among patients with a clinical history of CVD, but without hypertension, antihypertensive treatment was associated with decreased risk of stroke, CHF, CVD events, and all-cause mortality.

We do not know if benefits occur in patients without CVD.

JAMA March 2, 2011; 305:913-22 Original investigation, first author Angel M Thompson, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA.

An editorial in this issue of JAMA (pp 940-41) “Antihypertensive Therapy for Prehypertension” first author Hector O Ventura, Ochner Medical Center, New Orleans LA comments and expands on this article:

The definition of hypertension has evolved throughout the years. In the past, it was associated with the aging process, and BP levels equal or higher than 160/100<sup>1</sup> were considered abnormal. Twenty years ago, Frolich reported that BP higher than 140/90 is associated with increased risk of CVD, stroke and premature death. In 2003, the Joint Commission proposed the term “prehypertension” to designate a systolic BP of 120 -139 / 80-89.<sup>2</sup>

The classification was based on data from epidemiologic studies that demonstrated a linear relationship between BP and CVD risk. For each 20 mm Hg increase in systolic and 10 mm Hg in diastolic greater than 115/75, there was a 2-fold increase in mortality associated with stroke and coronary artery disease. Individuals with BP 120-139 / 80-89 are at risk of developing hypertension and CVD later in life compared with those with levels less than 120/80. The identification of patients with prehypertension will allow early intervention with lifestyle interventions to reduce BP, lessen progression to hypertension, and decrease risk of CVD morbidity and mortality.

Data from NHANES 2005-06 and other studies have demonstrated that the prevalence of prehypertension in the US population varies between 25% and 37%.

About 90% of individuals with prehypertension have at least 1 other cardiovascular risk factor above optimal levels, and 68% have at least 1 significant clinical risk factor for heart disease and stroke. Other studies have demonstrated that,

compared with normotensive individuals, 51% of men ,and 36% of women with prehypertension have higher levels of blood glucose, total cholesterol, LDL-cholesterol, triglycerides and body mass index and lower levels of HDL-cholesterol. <sup>3</sup>

The treatment of hypertension has evolved over the past century. In the early 1900s, there was controversy as to whether lowering BP was beneficial. In 1937 Paul D White (the preeminent cardiologist of the day) wrote that “ the treatment of hypertension itself is a difficult, and an almost hopeless task in the present state of our knowledge, and in fact for aught we know, in advanced cases with permanently narrowed coronary and cerebral arteries, the hypertension may have an important compensatory mechanism which should not be tampered with”.

Today, multiple clinical trials have demonstrated that, among patients with BP above 140/90, lowering levels with drugs and lifestyle interventions is associated with reduction in CVD mortality and morbidity. Interventions in patients with prehypertension have fielded disparate results.

1. In the early days, I often heard that normal BP is 100 plus your age.
- 2 The article stated prehypertension ranged from 130 -139/ 86-80. The JNC defines it as 120-139/80-89. This would define normal systolic BP as 115-119. Is this distinction important? I doubt it makes much difference. (Source Wikipedia and Mayo Clinic.)
- 3 This is where drug treatment should be deemphasized, not only on lowering BP.

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### **3-3 THE EFFECTS ON SURROGATES OF MAKING TREATMENT DECISIONS FOR OTHERS; Systematic Review**

Many adult patients near the end of life cannot make their own treatment decisions. Standard practice relies on surrogates to make decisions for them, typically in consultation with the patient’s physician.

If making treatment decisions has a negative psychological effect, it might impair a surrogate’s ability to protect patients who lack decision-making capacity, and would represent a harm to surrogates. In addition, it might conflict with the preferences of patients who do not want to be a burden to their family.

This review assessed the effects on surrogates of making treatment decisions for adults who cannot make their own decisions.

#### **STUDY**

1. Literature search identified 5221 possibly relevant studies. Of these, 40 met inclusion criteria.
2. Of these 40 studies of 2854 surrogates, 29 used qualitative data and 11 used quantitative data.

More than half of the surrogates were family members of the patients. Most were surveyed months to years after making the treatment decisions, the majority of which were end-of-life decisions (choosing to initiate, withhold, continue, or withdraw life-sustaining treatment).

## RESULTS

1. The quantitative studies found that at least one third of surrogates experienced a negative emotional burden as a result of their decision.
2. The qualitative studies reported that many or most surrogates experienced a negative burden. A study of 74 surrogates found that the stress levels were “extraordinarily high”, comparable to stress or a fire or construction disaster.
3. The negative effects on surrogates were often substantial and typically lasted for months or, in some cases, years. The most common effects cited were stress, guilt over the decision they had made, and doubt regarding whether they had made the right decision.
4. Surrogates of patients who had died in intensive care units frequently described their decision-making experiences as “difficult”, “intense”, “painful”, “devastating”, “overwhelming”, “traumatic”, and “the hardest thing that I have ever done in my life”. “The tremendous burden of medical decision-making ”
5. The most common reported stressor:
  - Unsure of the patient’s wishes
  - Uncertain prognosis
  - Discomfort with the hospital environment
  - Poor communication with the clinician
  - Insufficient time
  - Sense of sole responsibility
  - Uncertainty or guilt over decisions
6. Conversely, four studies reported that most surrogates were satisfied with their decision-making, and only 8% were either slightly or very dissatisfied. One study reported that those who were highly satisfied with the decision-making process still experienced a high degree of emotional burden. Nine studies also reported beneficial effects on a few surrogates--most commonly a feeling of satisfaction they were supporting the patient. Knowing which treatment is consistent with the patient’s preference were frequently cited as reducing the negative effect on surrogates.
7. A study of 16 Japanese Americans who had made end-of-life treatment decisions for family members found that making the decisions was very difficult, but the surrogates did not report any emotional burden. This may have been because most of the patients had made advance directives.
8. Nine studies reported that being involved in the decision-making process was beneficial to the

surrogates. The most common beneficial effects reported were positive feelings as a result of supporting the patient, and a sense of satisfaction. "I was honored to speak for him because I knew what he wanted."

9. The emotional burden on surrogates often lasted for months, and sometimes years. This was due primarily to 2 aspects of decisions-making:
  - 1) The process causes stress and anxiety. One study reported that surrogates repeatedly "searched their own sense of mortality about making a decision that could be interpreted as taking another's life." Some hoped that the patient would "die on his own" so they would not have to make a decision.
  - 2) Many surrogates expressed guilt and anxiety over whether they had made the right decision. "Did I do the right thing?"
10. The type of negative affect that surrogates experience seems to vary depending on the patient's circumstances and the nature of the decision. Those who decided to place the family member in a nursing care facility reported they had feelings of abandonment or betrayal.
11. Many studies found that the surrogate's experience is affected by the level of confidence in his or her knowledge of which treatment the patient would have wanted. There was greater confidence in the decision-making process when consensus was achieved regarding how the patient would want to be treated. Having the patient's advanced directive about treatment preferences substantially reduced surrogate stress. "Thank God Mom and Dad had a living will made." "I'm glad I was not the only person who had to make the decision" and "That's why I have no regrets. I was carrying out her wishes."
12. But some studies reported that having confidence in their knowledge of the patient's treatment preferences did not ease the burden. Some surrogates experienced a more negative emotional burden when the treatment that was thought to be in the patient's best interest differed from the treatment the patient would have wanted.
13. Confidence regarding the patient's treatment preferences was associated with more positive surrogate experiences.

## DISCUSSION

1. This analysis of more than 2800 surrogates indicates that decision-making places an emotional burden on at least one third of surrogates.
2. The most common negative effects cited were stress when making a decision, guilt over the decisions made, and doubt about whether they had made the right decision.

3. Negative emotional burdens can reduce the understanding and processing of complex information. This may undermine a surrogate's ability to make decisions that promote the patient's preferences.
4. By exposing surrogates to emotional burdens, current practice conflicts with patients' desire not to burden their loved-ones.
5. The data provide compelling evidence that knowing the patient's treatment preference substantially influences the effect on surrogates. Identifying which treatment option is consistent with the patient's preference could reduce the burden on surrogates.
6. The finding that poor communication increases the emotional burden highlights the importance of ensuring good communication between the clinician and families. Shared decision-making between clinician and family may help to decrease the burden on surrogates. Physicians, however, are less able to predict patient treatment preferences than the family.
7. There may be differences between ethnic groups and races in their approach to this problem.

## SUMMARY

Making treatment decisions for incapacitated loved ones places an emotional burden on at least one third of surrogates.

Being confident of which treatment the patient would want has an important protective effect for surrogates.

Methods for making treatment decisions would ideally promote at least 3 goals:

- 1) Identifying treatments that are consistent with the patient's preferences.
- 2) Respecting patient's preferences regarding how treatment decisions are made.
- 3) Protecting the patient's family and loved ones.

Annals Internal Medicine March 1, 2011; 154: 338-346 Original investigation, first author David Wendler, , National Institutes of Health. Bethesda, MD

Supported by the National Institutes of Health and by Institute of Biomedical Ethics, University of Zurich, Switzerland

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## **3-4 EFFICACY OF DRUG TREATMENT FOR GENERALIZED ANXIETY DISORDER: Systematic Review and Meta-analysis**

Generalized anxiety disorder (**GAD**) is a chronic or relapsing condition characterized by persistent and pervasive worrying and tension, which causes substantial personal distress and imposes a considerable economic burden.

Anxiety disorders are among the most prevalent of mental disorders and GAD is the most common and most impairing anxiety disorder in primary care. The degree of disability attributed to GAD compares with that of major depression and is similar to that of chronic physical illnesses such as arthritis and diabetes.

Current guidelines for drug treatment recommend first line treatment with a selective serotonin reuptake inhibitor or pregabalin.

This systematic review compared the efficacy and tolerability of all drug treatments by combining data from published randomized controlled trials.

The extracted data were combined in a series of mixed treatment meta-analyses, which incorporated evidence from trials, indirectly comparing drugs with a common comparator (such as placebo) as well as evidence from head-to-head trials. Application of this approach within a Bayesian framework enables treatments to be ranked in terms of the probability of each treatment being the first or most effective for each outcome measure.

## STUDY

1. This systematic review included only double blind, placebo- controlled randomized trials of any duration; and published systematic reviews and meta-analyses of randomized-controlled trials in adults receiving any drug for treatment of GAD. (1980-2009)
2. Extracted data consisted of treatments and dosage, methods for diagnosis of GADS, duration, and relevant outcomes (anxiety scores at baseline and end of study, and proportion of responders and remitters).
3. Using a modeling technique, treatments could be ranked by using probabilistic statements, and the probability of each drug being ranked first/most effective for each outcome measure.
4. Primary outcome measures:
  - 1) Response: The proportion of patients who experienced at least a 50% reduction from the baseline score on the Hamilton anxiety scale. (*Available on Google Ed.*)
  - 2) Remission: The proportion of patients with a final score 7 or less. (Of 56)
  - 3) Tolerability: Withdrawals because of adverse events.

## RESULTS

1. The search included 3249 potentially relevant publications. Only 27 met inclusion criteria and

contained sufficient or appropriate data.

2. The data from the 27 publications allowed analyses to be performed for 9 treatments: duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine, and venlafaxine
3. Used two different mixed treatment meta-analyses: 1) Bayesian probabilistic analysis, and 2) frequentist methods. This allowed both direct evidence (from head-to-head trials) and evidence from trials indirectly comparing drugs with a common comparator (eg, placebo) to be combined.
4. Probabilistic analysis of drugs by outcome measures.

(Figures in parentheses indicate percentage chance of being ranked first)

Rank	Response	Remission	Tolerability
1	Fluoxetine (63)	Fluoxetine (61)	Sertraline (49%)
2	Lorazepam (17)	Escitalopram (26)	Pregabalin (7%)*
3	Duloxetine (3)	Vnlafaxine (4)	Fluoxetine (38%)

4 - 9 All other drugs had a percentage probability of being first of 7% or less.

(\*I do not understand this rating )

5. All drugs were favored over placebo in all 3 categories
6. Response: Fluoxetine had the greatest probability of being the most efficacious treatment (63 % chance of being first.)
6. Remission: Fluoxetine was also ranked first (61% chance of being first)
7. Tolerability: Sertraline was ranked best with a 48% chance of being first for tolerability.) (Ie, was associated with the lowest probability of withdrawal). Fluoxetine was also rated high. (Ie, a lower probability of withdrawals.) Lorazepam was associated with the highest probability of withdrawals.

## DISCUSSION

1. Fluoxetine was rated first in terms of response and remission. Sertraline was first for tolerability.
2. All active treatments were favored over placebo. Placebo was favored over all treatments in terms of withdrawal.
3. “There were few significant differences between active treatments in terms of response and remission. As our primary probabilistic analysis did not rely on (*statistically*) significant outcomes, treatments could still be ranked in terms of effectiveness.”
4. “We analyzed extracted data using robust statistical methods and our primary probabilistic analysis. Using a Bayesian approach allowed treatments to be ranked in terms of the three outcomes measured. The Bayesian analysis allowed both direct and indirect data to be combined in a robust

and more intuitive way than in a standard frequentist analysis. Probabilities are easier to understand and interpret than P values. Although Bayesian analysis includes a subjective element, this has been minimized, and there was consistency between the direct and mixed treatment evidence.”

5. One weakness of the study was that all trials were sponsored by drug companies. But any bias would probably affect all drugs similarly.
6. As there was only one study involving fluoxetine, it is uncertain whether this study is an outlier because fluoxetine is the most efficacious drug, or if it is a positive outlier (high odds ratio) that is not matched with a negative outlier (low odds ratio).
7. Interpretation: The findings of this meta-analysis suggest that selective serotonin reuptake inhibitors are the most effective drug treatment option for patients with GAD.
8. This study could evaluate only the initial phase of treatment (6 to 8 weeks). GAD is regarded as a long term condition requiring long term treatment.

## CONCLUSION

In this study, fluoxetine was most effective in terms of response and remission, and sertraline was first in terms of tolerability.

BMJ March 19., 2011;342:637 Original investigation, first author David Baldwin, University of Southampton, Southampton, UK BMJ 2011;342:d1199

An editorial in this issue of BMJ (pp. 608-09) “Drug Treatment for Generalized Anxiety Disorder” by Toshi A Furukawa, Kyoto Graduate School of Medicine, Kyoto, Japan comments and expands on this article:

GAD is characterized by excessive worrying over everyday things and is associated with irritability; restlessness; difficulty in concentrating; and somatic symptoms such as muscle tension, fatigue, and sleeplessness. GAD first appeared in the American diagnostic classification system in 1980 as a residual category after diagnostic criteria for much more specific anxiety disorders such as panic disorder, phobias, and obsessive-compulsive disorder had been delineated. It is now generally recognized as an independent diagnostic entity. It can be distinguished from other, often coexisting, mental disorders and its symptoms are uniquely associated with functional impairment and distress. It is common.

Various drugs, in addition to cognitive behavioral therapy, have been shown to be effective. But, which one is likely to be the most effective and acceptable for the patient?

A more refined use of available evidence is now possible. Multiple treatment meta-analysis (also known as mixed treatment comparison, or network meta-analysis) is a relatively new approach to systematic reviews, which combines evidence from both direct head-to-head comparisons and indirect comparisons via

intermediate comparators (such as placebo). It preserves the comparison of randomized treatments within each trial and offers many advantages:

- 1) It can produce tighter confidence intervals than found with other analyses because it uses both direct and indirect estimates.
- 2) It can estimate relative effectiveness between treatments that have never been directly compared.
- 3) When conducted within a Bayesian framework, it can rank treatments on the basis of the probability of each treatment being the best among all alternatives.

Although the authors make best possible use of available evidence, some limitations should be noted. Only half of the trials included contributed to the multiple treatment meta-analysis for response, and fewer than one third for remission. Fluoxetine was ranked first based on data from only one trial of 33 patients. Few (*statistically*) significant differences were seen in terms of response among active treatments. The evidence for these relative rankings should be downgraded two or three levels for publication bias, imprecision, inconsistency, and indirectness.

With these caveats in mind, evidence suggests that fluoxetine, and sertraline have some advantages over the short term. However, the weaknesses noted make it difficult to draw firm conclusions.

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### **3-5 GLUCAGON-LIKE PEPTIDE-1 ANALOGUES FOR TYPE 2 DIABETES: A Review Article**

Glucagon-like peptide-1 (**GLP-1**) is a naturally occurring peptide hormone released from the gut after eating.

GLP-1 has several important functions: 1) stimulates insulin secretion; 2) suppresses glucagon release (thereby reducing hepatic gluconeogenesis); 3) delays gastric emptying and promotes satiety.

Its has a short half life (minutes) as a result of rapid breakdown by endopeptidases.

Two GLP-1 analogues (also known as incretin mimetics) are available for treatment of type-2 diabetes (**DM-2**) : exenatide and liraglutide. These are modified GLP-1 peptides which resist downgrading by endopeptidases. Their half-life is extended.

They are indicated as adjuncts to other treatments for DM-2.

Exenatide: (*Byetta*; Amylin Pharmaceuticals and Eli Lilly)

Elimination half-life is 2.4 hours. It is given twice daily by subcutaneous injection.

Several randomized-controlled trials have been published comparing exenatide given for 6 months with combinations of other drugs (sulphonylureas, metformin, and thiazolidinediones) and the same drugs given with placebo.

Exenatide was associated with a consistent 0.9% lowering of HbA1c levels compared with placebo. The number needed to treat to achieve a level of under 7% ranged from 3 to 6. Body weight fell significantly by 1.3 kg compared with placebo. Some patients continued to lose weight and maintained the lowering of HbA1c as an “open label” phase of the study continued for up to 3 years.

When exenatide was compared with insulin, the HbA1c level was no lower, but patients were more likely to lose weight, while insulin patients gained weight.

Current guidelines from the American Diabetes Association support its use as an alternative third-line treatment for overweight and obese patients. But more established options such as insulin, for which outcomes data are available, are preferred.

UK guidelines recommend considering exenatide in addition to sulphonylureas and metformin for patients with BMI over 35, or if insulin treatment is unacceptable. Treatment should continue after 6 months only if the HbA1c has fallen by at least 1% and body weight is reduced by at least 3%.

#### Liraglutide (*Victoza*; Novo Nordisk)

Elimination half-life is 12 hours. It is given once daily by subcutaneous injection.

Clinical trials include a comparator trial vs glimepiride and a placebo-controlled trial in patients taking metformin or sulphonylurea, with and without thiazolidinediones.

The number needed to treat to achieve a HbA1c of less than 7%, when added to metformin, compared with placebo added to metformin was 3.

Add-on trials have compared liraglutide with placebo or insulin in patients poorly controlled with dual therapy of metformin and sulphonylurea. These trials have shown that liraglutide significantly improved glycaemic control.

One trial compared liraglutide with exenatide over 6 months. High doses of liraglutide were better at lowering HbA1c (1.12% vs 0.79%), and were associated with fewer reports of nausea (3% vs 9%).

A longer term follow-up of the trial, in which patients taking exenatide were switched to liraglutide for an additional 6 months, showed further improvement in glycaemic control (mean fall in HbA1c of 0.32% and body weight of 0.9 kg). A recent UK appraisal recommended use of 1.2 mg dose with the same stopping criteria as with exenatide.

#### Safety:

Nausea or vomiting, or both, affect 30% to 60%, although only 5% discontinued clinical trials due to gastrointestinal side effects. This provides the rationale for dose-titration regimens used with both

agents, and probably explains why few of these events led to withdrawal. Liraglutide (likely because of its slowed onset of action and longer half life) may be slightly less problematic in this regard.

Reactions at the injection sites were uncommon.

Thirty eight percent of exenatide patients developed antibodies. Most were of low titer and did not seem to influence the therapeutic effect, but about 6% had higher titers. About half of these did not show any improvement in HbA1c.

The frequency of hypoglycemia in those taking GLP-1 analogues is similar to those taking placebo. However, among those taking metformin and/or thiazolidinediones, hypoglycemia may occur more frequently in those who also take a sulphonylurea. This may require a dose reduction in the sulphonylurea when starting treatment.

Currently, no data are available for long-term safety of treatment incorporating GLP-1 analogues.

#### Precautions:

Do not use in patients with an estimated glomerular filtration rate lower than 30%. Liraglutide is not recommended for patients with moderate renal impairment (estimated glomerular filtration rate under 60%)

Caution in using for patients with a history of pancreatitis (or at high risk of pancreatitis as with hypertriglyceridemia). Several cases have been reported in patients taking GLP-1 analogues.

Neither drug has been formally studied combined with insulin. Neither is licensed for use with insulin.

Neither drug should be used in patients who are severely insulinopenic (eg for patients who are losing weight rapidly with poor glycemic control, particularly if ketones are present).

#### How should they be given?

Both are given from prefilled pen injection devices.

Exenatide is given twice daily up to 2 hours before meals, and at least 6 hours apart.

Liraglutide is given once daily, at any time of the day, but at the same time each day.

Dose titration is required to help initial nausea. For exenatide, half the maximum dose is given for a month before titrating up to the full dose.

Liraglutide is titrated weekly. Most patients require doses up to the second highest dose of the 3 doses available.

Regular home glucose monitoring is recommended when used in combination with sulphonylureas because of risk of hypoglycemia.

Monitor weight, BP, lipids periodically, as with any patient with diabetes.

The future of GLP-1 drugs will depend on:

Evidence of cardiovascular safety and long-term benefits on micro-vascular and macro-vascular complications.

Whether the compounds can preserve beta-cell function.

The development of longer lasting analogues. (*Long-acting preparations are available for both drugs. Ed*)

Cost

These drugs are expensive, ranging from \$312 to \$503 for one month's supply, depending on dose.

BMJ February 19, 2011; 342: 433-36 "Therapeutics", first author John P H Wilding, University of Liverpool, UK