PRACTICAL POINTERS

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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.

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 20-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 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* OCTOBER 2008

If You Are A Heavy Smoker And Live To Age 70, You Will Feel 10 Years Older

10-1 THE EFFECT OF SMOKING IN MIDLIFE ON HEALTH-RELATED QUALITY OF LIFE IN OLD AGE: A 26-Year Prospective Study

Smoking shortens life expectancy by 7 to 10 years. Do smokers who survive experience more years of disability? Are the extra-years gained by not smoking related to a better health-related quality of life (**HRQoL**)?

This prospective cohort study followed over 1100 men for 26-years. All were healthy at baseline in 1976 (mean age 48). About 1/3 were non-smokers; 2/3 smokers.

Determined total mortality through 2000 and HRQoL of survivors (mean age 73) in 2000.

During follow-up, 22% died. Never-smokers lived a mean of 10 years longer than heavy smokers.

In 2000, only 78 subjects (7%) were still smoking.

There was a graded deterioration of HRQoL with increasing number of cigarettes smoked.

Never-smokers had the highest (best) scores on all 8 of the RAND-36 scales There were especially large differences in the scales of physical functioning, and in role limitations compared with those who smoked over 20 /d (differences = +17% and +16%).

The 78 subjects who survived and continued to smoke in 2000, had poorer scores in all 8 scales compared with the other categories of smokers.

Although many smokers had quit between baseline and 2000, the effect of baseline smoking on mortality and HRQoL in old age remained strong.

Cigarette smoking had a dose-dependent effect on mortality and the RAND scale. Heavy smokers had the worse results for both end points.

"Compared with heavy smokers, never-smokers had a mean life expectancy that was 10 years longer. They also enjoyed significantly better physical health status, which was equal to an age difference of 10 years"

Conclusion: During a 26-year follow-up, HRQoL deteriorated with an increase in daily cigarettes smoked in a dose-dependent manner. Never smokers lived longer and their extra years were of better quality.

I was impressed with the number of subjects who quit smoking. Does Finland have a superior quit program?

At baseline (mean age 48) smokers had worse perceived health and physical fitness than non-smokers. Perceptions of worse perceived health declined as number of cigarettes smoked increased.

I presume many began to smoke in adolescence.

Smokers do not experience any increase in the pleasure of living.

Does smoking ever bring benefits? Some who survived extreme stress (eg, war) have stated that they could not have survived without the comfort of cigarettes.

Women with A Negative HPV Test May Safely Be Screened Every 6 Years.

10-2 LONG TERM PREDICTIVE VALUES OF CYTOLOGY AND HUMAN PAPILLOMAVIRUS TESTING IN CERVICAL CANCER SCREENING

Seven primary screening studies included over 24 000 women. All routinely used both cytology and HPV tests. Included only women with adequate cytology and HPV tests at baseline, and with at least one follow-up cytological test. Cytology tests in Europe are commonly recommended every 3 years.

Regarded abnormal cytology as the equivalent of atypical squamous cells of uncertain significance or worse.

Of the original 24 295 women, 381 developed confirmed cervical cancer during 6 years of follow-up.

Cumulative incidence of cervical cancer at 6 years (% per 10 000 subjects):

HPV + / cytology +	34	
HPV + / cytology -	10	
HPV - / cytology +	2.7	(ten patients)
HPV - / cytology -	0.27	(one patient)

The cumulative incidence of cancer in those HPV + rose continuously over 6 years. The cumulative rate of cancer in those positive for cytology & negative for HPV remained below 3%.

In patients negative for both tests, the cumulative incidence rate of future cancer during 6 years of follow-up was uniformly low. Double negativity confers a long lasting protective effect.

Conclusion: The consistently low 6-year cumulative incidence rate of cervical cancer among women with a negative HPV test suggests that screening intervals for HPV could safely be lengthened to 6 years. This could at least partially compensate for the increased referral rate resulting from the higher false positive rates of HPV-based screening strategies, especially in younger women.

Both CIN and HPV can regress. The latter due to development of immunity, especially in younger women.

I believe both tests should be dome simultaneously. Note that if both are positive, the rate of progression to cancer over 6 years was about 3 out of 10.

The tests are more predictive in older women.

Associated With Less Aggressive Medical Care And Earlier Referral To Hospice

10-3 ASSOCIATIONS BETWEEN END-OF-LIFE DISCUSSIONS, PATIENT MENTAL HEALTH, MEDICAL CARE NEAR DEATH, AND CAREGIVER BEREAVEMENT ADJUSTMENT.

End-of-life discussions (**EOLD**) offer patients the opportunity to define their goals and expectations for the medical care they want to receive near death. These discussions mean confronting the limitations of medical treatments and the reality that life is finite, both of which may cause psychological distress. Talking about death can be difficult.

This study examined the associations between EOLD and the medical care terminally ill cancer patients receive. (Patients with advanced cancer who prefer life-extending therapy are often overly optimistic about their chances of survival.) Do EOLD benefit or harm? Do they lead to fewer aggressive interventions?

The study (2002-08) included 332 patients who died of incurable cancer. It examined the medical care they received in the final week of life, and assessed caregiver's quality-of-life (**QOL**) at a median of 6 months later, at a point that they would likely be beyond acute grief.

At a baseline interview patients were asked "Have you and your doctor discussed any particular wishes you have about care you want to receive if you were dying?"

EOLD were not associated with patients being depressed, sad, or worried.

Patients who engaged in the discussion were more likely:

To accept that their illness was terminal

To prefer treatment focused on pain and discomfort over life-extending treatment

To have completed a do-not-resuscitate order

To receive fewer aggressive interventions

To be enrolled in hospice for more than a week

Were less likely to receive ventilation, undergo resuscitation, and to be admitted to intensive care

Bereavement outcomes:

A direct relationship existed between patients' QOL near death and their bereaved caregivers' QOL

Caregivers of patients with high QOL felt better prepared for the death and experienced less

regret at follow-up

Caregivers of patients who received aggressive care:

Were at higher risk of developing a major depressive disorder

Were at higher risk of feeling unprepared for the patient's death

Experienced worse QOL, more regrets, and were at higher risk of developing a major depressive disorder 6 months later

QOL improved the longer the patient was enrolled in hospice. Patients who received less than a week of hospice care had the same QOL scores as patients who received no hospice care, suggesting that patients benefit more from early hospice referral.

The association between EOLD and patients' preferences for less aggressive care is noteworthy. EOLD may make patients more realistic about benefits of aggressive therapies.

By acknowledging that death is near, patients, caregivers, and physicians can focus on clarifying patients' priorities and improving pain and symptom management.

Conclusion: End-of-life discussions are associated with less aggressive medical care and earlier hospice referrals. Aggressive care is associated with worse quality-of-life and worse bereavement adjustment.

I believe this article will be helpful to many primary care clinicians and their patients. Compared with the past, more terminally ill patients accept death as a normal part of life. Death at an advanced age is not the taboo it once was. Death at an early age may be much more distressing. The goal is to lengthen the period of good quality of life and compress the period of bad quality.

To some, dying may be a time of reflection, forgiveness, and acceptance.

There are, however, cultural differences which clinicians should be aware of. The article noted that many participants were of ethnic minorities.

Many clinicians may find it difficult to talk to individual patients about impending death. And have difficulty in broaching the subject. The closer the pateint-physician relationship, the easier the conversation will become.

A simple question "Are you at peace" may be an introduction.

"A Strategy With Substantial Benefits"

10-4 EFFECTIVENESS OF MATERNAL INFLUENZA IMMUNIZATION IN MOTHERS AND INFANTS

Inactivated flu vaccine is recommended for pregnant women. It is not licensed for infants younger than age 6 months. It is licensed for age 6 to 23 months. Anti-viral drugs for influenza are not licensed for infants under age 1 year.

This study assessed the clinical effectiveness of the inactivated vaccine administered during pregnancy.

Over a 17-month follow-up:

	Laboratory-confirmed influenza
Infants of vaccinated mothers (n = 172)	6 cases
Infants of mothers not vaccinated (n = 168)	16 cases
(Vaccine effectiveness for infants was 63%)	
	Respiratory illness with fever
Infants of vaccinated mothers (n = 172)	110 cases
Infants of mothers not vaccinated (n = 168)	153 cases
(Vaccine effectiveness 29%)	

Among mothers, respiratory disease with fever was reduced by 36% compared with the non-vaccinated.

Clinical effectiveness in infants lasted up to 6 months of age.

The absolute reduction in the rate of illness showed that every 100 immunizations prevented respiratory illness with fever in 14 infants and 7 mothers. Five mothers would have to be vaccinated to prevent a single case of respiratory illness with fever in a mother or infant.

Conclusion: Inactivated influenza vaccine reduced proven influenza illness by 63% in infants up to 6 months of age and averted approximately a third of all febrile respiratory illnesses in mothers and young infants.

Another illustration of why almost everyone should be immunized against influenza.

Metformin Moderately Protective; Rosiglitazone Possibly Harmful.

10-5 CARDIOVASCULAR OUTCOMES IN TRIALS OF ORAL DIABETES MEDICATIONS

Improvements in control of glucose levels have been shown to reduce incidence of *micro*vascular disease. The effect on long-term cardiovascular (macrovascular) complications is not clear.

This literature search found 40 randomized controlled trials that reported *macro*vascular outcomes and mortality associated with second-generation sulfonylureas, biguanides, thiazolidinediones, and meglitinides for treatment of type-2 diabetes (**DM-2**).

Risk of fatal and non-fatal cardiovascular disease (**CVD**) and all-cause mortality:

A. Metformin vs placebo or other oral agents for cardiovascular mortality (7 trials)

Overall pooled odds ratio = 0.85 favoring metformin.(CI = 0.68-1.05)

B. Any sulfonylurea vs placebo or other oral agent (5 trials)

Overall pooled odds ratio = 0.89 favoring sulfonylurea (CI = 0.69-1.11)

C. Rosiglitazone vs placebo or other oral agents (5 trials)

Overall pooled odds ratio = 1.69 favoring placebo or other agents (CI = 0.51-6.11)

D. Pioglitazone vs placebo or other oral agents (6 trials)

Overall pooled odds ratio = 0.86 favoring pioglitazone (CI = 0.78-1.00)

Metformin was the only drug associated with a significant *decrease* in mortality. Rosiglitazone was the only drug associated with a possible *increase* in risk of cardiovascular morbidity or mortality.

"The poor quality and inconsistent reporting of adverse events and the profound lack of long-term studies make it difficult to draw firm conclusions." The reduction observed when intensive control was compared with conventional treatment suggests that glycemic control per se may be partially driving cardiovascular risk reduction.

Conclusion: Compared with other oral agents, metformin appears moderately protective against cardiovascular effects. Rosiglitazone is possibly harmful.

Epidemiological studies have reported a linear relationship between HbA1c and risk of CVD in type-2 diabetes. It would seem reasonable that reductions in HbA1c would reduce risk. Despite many trials, the association has not been established. There is a glimmer of hope from metformin.

Two recent trials of oral drugs reported no benefit, and possible harm.

We await information about effects of the incretin drugs and insulin.

Primary care clinicians can reassure patients that reducing HbA1c as much as possible, determined by individual ability to comply with a defined drug regimen and incidence of hypoglycemia, will reduce risk of microvascular complications. The American College of Physicians Guidelines (Annals Int Med September 18, 2007; 147: 417-22) recommends:

To prevent microvascular complications of diabetes, the goal for glycemic control should be as low as feasible without undue risk for adverse effects, or an unacceptable burden on patients.

Treatment goals should be based on a discussion of the benefits and harms of specific levels of

glycemic control with the patient. A HbA1c level less than 7%, on individualized assessment, is a reasonable goal for many, but not all patients.

Protection against CVD complications of DM-1 depends much more on standard risk-lowering intervention (lipid, BP, and weight control; smoking cessation; and maintaining physical fitness) than on control of HbA1c.

Increases In Levels Of Insulin, Not Glucose, May Be Etiologic

10-6 GLUCOSE LOWERING TO CONTROL MACROVASCULAR DISEASE IN TYPE-2 DIABETES

Whether reduction of cardiovascular risk results from intensive glycemic control in DM-2 remains an unanswered hypothesis. A recent large trial of intensive treatment of DM-2 was stopped early because of an increase in total mortality. Other trials have failed to provide evidence that intensive glucose control leads to cardiovascular protection.

Numerous trials have demonstrated that high levels of HbA1c and glucose are predictors of cardiovascular disease. The relationship of glucose levels to cardiovascular disease mortality is especially strong in patients with established cardiovascular disease.

This may be explained by insulin resistance or hyperinsulinemia. In large population-based studies, insulin levels predict increased cardiovascular risk. High fasting insulin concentrations have been reported to be an independent predictor of ischemic heart disease. This raises the possibility that increases in levels of insulin, not glucose, may be etiologic in cardiovascular disease. Insulin has mitogenic effects on vascular smooth muscle and increases activity of plasminogen activator inhibitor, thereby decreasing fibrinolytic activity.

“If insulin levels are toxic to the cardiovascular system, then treatments designed to reduce insulin levels, rather than glucose levels, might be associated with a reduced risk of cardiovascular events in patients with type-2 diabetes.”

“It may be appropriate to focus on the aggressive control of insulin levels or insulin resistance rather than only on aggressive control of glucose levels.”

To my knowledge, only metformin and lifestyle interventions decrease insulin levels.

The large trial mentioned is the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes” (NEJM 2008; 358: 2560-72). Over 90% of participants were receiving rosiglitazone. This drug may have caused some of the adverse cardiovascular events.

I abstracted this article because it is provocative. I will look for further studies regarding possible toxicity of insulin

Similar Glycemic Control Occurred With NPL or IG When Added To Oral Regimens

10-7 ADDITION OF NEUTRAL PROTAMINE INSULIN LISPRO OR INSULIN GLARGINE TO ORAL TYPE-2 DIABETES REGIMENS FOR PATIENTS WITH SUBOPTIMAL GLYCEMIC CONTROL

Glycemic control, preferably to HbA1c levels less than 7%, can substantially reduce the risk of *micro*vascular, and possibly *macro*vascular complications in patients with type-2 diabetes (**DM-2**). Maintaining such levels is now recommended for clinical practice, but it is difficult to achieve despite escalating doses of oral drugs.

Most patients withDM-2 eventually require insulin added to oral agents as glycemic control becomes suboptimal. A single bedtime injection of a long-acting insulin added to oral agents is then the preferred treatment worldwide.

This study compared the clinical efficacy and safety of bedtime neutral protamine lispro (**NPL)** and insulin glargine (**IG)** added to ongoing oral therapy with stable doses of metformin and sulfonylureas in patients with DM-2. All had suboptimal control.

Randomized to 10 IU of NPL or IG at bedtime. Adjusted dose of insulin to target fasting glucose less than 100 mg/dL. Oral agents were continued at the pre-study doses. But, only metformin was permitted at the evening meal in order to minimize risk of sulfonylurea-induced nocturnal hypoglycemia.

HbA1c improved equally in both groups (- 1.8%), reaching a plateau after 12 to 24 weeks.

Secondary outcomes did not differ between groups: HbA1c levels below 7% (62%); fasting plasma glucose < 100 mg/dL (40%); insulin dose; and body weight.

Hypoglycemia:	NPL	IG
Any hypoglycemic event:	74%	67% (About 6 episodes per year per patient)
Symptomatic hypoglycemia	45%	40%
Nocturnal hypoglycemia	33%	25%
Severe hypoglycemia	0	0

"The results of our study confirm the feasibility of adding basal insulin to oral antihyperglycemic drugs, with intensive dose titration as a strategy for achieving recommended glycemic targets in patients with poorly controlled type-2 diabetes."

Conclusion: Bedtime IG or NPL added to oral medication in patients with poorly controlled DM-2 resulted in similar glycemic control.

The study reports surrogate outcomes—no clinical outcomes.

Poor control of DM-2 is a risk factor for micro-vascular disease. The relation with macro-vascular disease is less clear. Is an increased risk of hypoglycemia worth an indefinite lowering of risk of macro-vascular complications? Some recent trials have reported an increase in cardiovascular disease related to intensive glycemic control, possibly due to insulin toxicity. Only metformin and life-style interventions will improve glycemia without increasing insulin levels.

The usual methods of lowering macro-vascular risk (lipid, BP, and weight control, exercise, and possibly low dose aspirin) would likely lower risk much more than strict control of HbA1c.

A Legacy Effect

10-8 10-YEAR FOLLOW-UP OF INTENSIVE GLUCOSE CONTROL IN TYPE-2 DIABETES.

The original United Kingdom Prospective Diabetes Study (**UKPDS**) enrolled patients from 1977 to 1991, and was reported in 1998. At baseline, over 4200 patients with newly diagnosed type-2 diabetes (**DM-2**) were randomized to: 1) dietary restriction, or 2) intensive therapy with sulfonylurea, or insulin, or to metformin (in overweight patients). It reported that patients who received intensive sulfonylurea-insulin therapy had a lower relative risk of *micro*-vascular complications than did those receiving conventional dietary therapy, and a non-significant reduction of 16% in myocardial infarction (**MI**). In overweight patients who primarily took metformin, the relative risk of MI was reduced by a statistically significant 39%, and risk of death from any cause was reduced by 36%.

This post-trial study monitored over 3200 of the UKPDS patients for an additional 10 years (1998 2007). No attempt was made to maintain their previously assigned therapy. Examined clinical outcomes on an intention-to-treat basis, according to the previous randomization categories.

Between-group differences in HbA1c were lost after the first post-trial year.

In the sulfonylurea-insulin groups, during the post-trial period, as compared with dietary restriction, statistically significant relative risk reductions persisted for any diabetes-related end point (9%); diabetes-related death (17%); myocardial infarction (15%); death from any cause (13%); and microvascular disease (24%), There were no significant risk reductions in stroke or peripheral vascular disease.

In the metformin group, as compared with the dietary restriction, statistically significant relative risk reductions persisted for any diabetes-related end point (21%), diabetes-related death (30%); MI (33%), and death from any cause (27%). There were no significant reductions in microvascular disease, stroke, or peripheral vascular disease.

Conclusion: Despite early loss of differences in HbA1c, a continued reduction in microvascular risk and myocardial infarction and death from any cause was observed during 10-years of post-trial follow-up.

Metformin (given to overweight patients) was superior to both sulfonylurea and insulin in reducing risk of any diabetes-related endpoint, diabetes-related death, myocardial infarction, and death from any cause during the period of the original trial and for 10 years thereafter.

Fortunately we have many more effective interventions to lower risk of cardiovascular disease than reduction in HbA1c. Since DM-2 is a strong risk factor, all patients with DM-2 should receive them.

Sulfonylurea-insulin was superior in reducing relative risk of microvascular disease.

If metformin reduced HbA1c levels over the years, why was microvascular disease not lowered?

Would the benefits be even greater if the reductions in HbA1c levels had been continued during 1998-2007 ?

Regarding micro-vascular complications: The association between poor glycemic control and risk of microvascular complications (neuropathy, retinopathy, and diabetic kidney disease) is well established.

Regarding macro-vascular complication: Good glycemic control does reduce risk to some extent. There are also other interventions which reduce risk of vascular complications to a greater extent (lipid control, BP control, low-dose aspirin, physical fitness, and weight control).

I believe the latter interventions will reduce vascular complications to a greater extent than good glycemic control, with fewer adverse effects and increased patient-compliance and satisfaction. We should cautiously control glucose levels as well as possible while avoiding the adverse effect of hypoglycemia.

A Promising Treatment Option

10-9 EXENATIDE ONCE WEEKLY VERSUS TWICE DAILY FOR THE TREATMENT OF TYPE-2 DIABETES

Incretins are hormones normally produced by the upper gastrointestinal tract after eating, even before the blood glucose rises. They have multiple glucoregulatory effects: enhancement of glucose-dependent insulin secretion, reduction of glucagon secretion, reduction of food intake, and slowing of gastric emptying. As a result, plasma glucose levels are reduced.

Glucagon-like-peptide-1 (**GLP-1**) fulfills the criteria for an incretin. It is rapidly inactivated by a peptidase. It is not clinically useful. It must be administered by continuous subcutaneous infusion.

Exenatide is a GLP-1 analogue (an incretin mimetic), a 39-amino-acid peptide bearing a 50% amino-acid homology to GLP-1. It displays biological properties similar to human GLP-1. Its half life is over 2 hours. It is produced by chemical synthesis.

Exenatide significantly improves glycemic control in patients suboptimally controlled by commonly used oral agents including metformin, sulfonylureas, and thiazolidinediones. The exenatide currently available requires twice daily subcutaneous injections. It does not provide continuous activation of receptors.

A long-acting form of exenatide has been developed for once-weekly injection. The sustained-release formulation (SRF-exenatide**; SRFE**) consists of microspheres of exenatide combined with a common biodegradable medical polymer, which has established use in absorbable sutures and extended release pharmaceuticals. This allows gradual drug delivery in a controlled rate.

This study compared safety and efficacy of the SRFE given once-weekly with that of the older preparation given twice daily in patients with DM-2.

All patients were receiving metformin, a sulfonylurea, a thiazolidinedione, or any combination of two of these or were naïve to oral drugs. Oral drugs were continued.

Outcomes at 30 weeks (mean;	SRFE	Twice daily
Reductions in HbA1c	1.9%	1.5%
HbA1c 7% or less	77%	61%
Fasting glucose mg/dL	- 41 mg/dL	- 25 mg/dL
Weight loss	- 3.6%	- 3.7%

Postprandial plasma glucose and glucagon levels were lower in the SRFE group.

Adverse effects:

Nausea was common (34%); vomiting (18%), predominantly mild.

No episodes on major hypoglycemia, irrespective of background sulfonylurea use.

Withdrawals due to adverse events were 6.1% for once weekly and 4.8% for twice daily.

Conclusion: Exenatide once-weekly resulted in greater improvements in glycemic control than exenatide given twice daily, with no increase in risk of hypoglycemia and with similar reductions in body weight.

This is not a practical point at this time. SRFE is not yet available. I abstracted the article because SRFE may be a significant advance.

If the preparation becomes available, I believe primary care clinicians should abide by the general rule for new drugs and wait a few years to be assured of adverse effects before prescribing it.

Currently Imperfect, But Promising

10-10 STOOL DNA AND COLON CANCER PREVENTION

Historically, screening approaches have sought to detect established colo-rectal cancer. The identification of precancerous adenomatous polyps is clearly preferable.

Guidelines now emphasize detection of precancerous polyps as the most effective strategy to prevent death from CRC. Colonoscopy is recommended. Testing for occult blood in the stool is notoriously insensitive.

The adenoma-to-carcinoma sequence in colon cancer is based on the stepwise progression of specific genetic alterations that parallel the histopathologic progression from pre-neoplasia to neoplasia. Detection of gene mutations in tumor cells sloughed off into stool is possible. Two DNA tests are available—Stool DNA Test-1 (**SDT-1**) and more recently **STD-2.** The latter assay includes 3 genes which are classically mutated at the stage of precancerous adenomas.

STD-2 is much more promising—46% of screen relevant neoplasms had a positive result. (Sensitivity = 46%) This would miss more than half of screen-relevant neoplasms. There are many false positives—16% to 26% of those tested positive did not have a neoplasm. Such high false positive rates would be problematic for population-wide screening.

For those unwilling to have a screening colonoscopy, a stool DNA could provide a noninvasive option that is superior to conventional occult blood testing.

I believe, at present, there is no substitute for optical colonoscopy.

10-11 WHAT HAPPENED TO THE POLYPILL?

In 2003, Wald and Law published an article describing a "polypill" which they stated would reduce incidence of heart attacks and stroke by 80%. The pill was to be taken by everyone over the age of 55 without pre-testing or follow-up. It contained aspirin, a statin, a diuretic, a beta-blocker, an ACE inhibitor, and folic acid—all generics and at low dose. The logic was that most people in Western society are at increased risk of cardiovascular disease, and that the drugs are effective and safe.

Now, more than 5 years later, you might imagine that research groups would be competing to test this innovative suggestion. Not so.

The polypill concept is accused of medicalizing the population. Wald argues that if you test people to see if they have high BP or high cholesterol, they are given a disease label and then must come back regularly to recheck. "You have created a patient." This is real medicalization—not universal access to a pill.

Does Wall sense a moral objection to use of the pill? He responds: "Is getting a vaccination a moral weakness?"

I have been fascinated by the polypill concept. It is based on the belief that all persons are at risk of cardiovascular disease. It continues to attract commentary. It seems to me that that a form of the polypill is already being taken by millions of Americans—low-dose aspirin, statins, antihypertensives, beta-blockers, and ACE inhibitors. But not over the counter, and not in one pill. Modern primary care requires a risk factor to be demonstrated objectively. Drugs are prescribed after tests establish risk, and require periodic follow-up. This magnifies costs and inconvenience.

Some will say that the pill medicalizes the whole population. Is not the whole population being largely medicalized now?

I believe that it takes only a glance to assess millions of persons in this country as being at risk.

I also believe there is little chance that the polypill concept will be tested or approved in the US. There is no commercial interest.

Could not, and should not, primary care clinicians legitimately prescribe a polypill to select patients?

ABSTRACTS OCTOBER 2008

If You Are A Heavy Smoker And Live To Age 70, You Will Feel 10 Years Older

10-1 THE EFFECT OF SMOKING IN MIDLIFE ON HEALTH-RELATED QUALITY OF LIFE IN OLD AGE: A 26-Year Prospective Study

Smoking shortens life expectancy by 7 to 10 years. Do smokers who survive experience more years of disability? Are smokers right when they defend their habit by declaring that they prefer a merrier, albeit a shorter life? Are the extra-years gained by not smoking related to a better health-related quality of life (**HRQoL**)?

This study examined the effect of long-term smoking in midlife on HRQoL in old age.

Conclusion: After years of smoking, HRQoL deteriorated to a greater extent in smokers than non-smokers.

STUDY

1. Prospective cohort study followed over 1600 men for 26-years. All were healthy at baseline in 1976 (mean age 48).
2. Evaluated subjects in 2000 with the RAND Health Survey—1131 responded. Assessed cardiovascular risk factors, mortality, morbidity, and HRQoL.
2. Smoking habits at baseline:

Never smokers	614
Ex-smokers	650
1-10 cigarettes/d	87
11-20/d	119
> 20/d	188

3. Determined total mortality through 2000 and HRQoL of survivors (median age 73) in 2000.

RESULTS

1. During follow-up, 22% died.
2. Never-smokers lived a mean of 10 years longer than heavy smokers.
3. During follow-up, many smokers quit. (69% of those smoking more than 20/d, and 82% of those smoking 1 to 10/d). In 2000, only 78 subjects (7%) were still smoking.
4. There was a graded deterioration of HRQoL with increasing number of cigarettes smoked.
5. Never-smokers had the highest (best) scores on all 8 of the RAND-36 scales There were especially

large differences in the scales of physical functioning, and in role limitations compared with those who smoked over 20 /d (differences = +17% and +16%). The difference in physical functioning equaled an age difference of 10-years when compared with the age and sex-matched population.

7. The physical component summary score showed a graded deterioration of HRQoL with an increasing number of cigarettes smoked.
8. Ex-smokers did not generally reach as high a score as never smokers.
9. The 78 subjects who survived and continued to smoke in 2000, had poorer scores in all 8 scales compared with the other categories of smokers.

DISCUSSION

1. Although many smokers had quit between baseline and 2000, the effect of baseline smoking on mortality and HRQoL in old age remained strong.
2. Cigarette smoking had a dose-dependent effect on mortality and the RAND scale. Heavy smokers had the worse results for both end points.
3. The relatively few heavy smokers who survived to 2000, and were still smoking, had a worse HRQoL than current non-smokers.
4. The study included only men with higher social status. These results cannot be extrapolated to women and persons with lower social status.
6. “Compared with heavy smokers, never-smokers had a mean life expectancy that was 10 years longer. They also enjoyed significantly better physical health status, which was equal to an age difference of 10 years in the general population.”

CONCLUSION

During a 26-year follow-up, HRQoL deteriorated with an increase in daily cigarettes smoked in a dose-dependent manner. Never smokers lived longer and their extra years were of better quality.

Archives Int Med October 13, 2008; 168: 1968-74 Original investigation, first author Arto Y Strandberd, University of Helsinki, Finland

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Women with A Negative HPV Test May Safely Be Screened Every 6 Years.

10-2 LONG TERM PREDICTIVE VALUES OF CYTOLOGY AND HUMAN PAPILLOMAVIRUS TESTING IN CERVICAL CANCER SCREENING

Tests of human papilloma virus (**HPV**) are more sensitive than cytology to detect high-grade cervical intraepithelial neoplasia (**CIN**).

This study obtained data from seven HPV screening studies, which investigated the long-term predictive value of primary HPV screening for future cervical cancer.

Conclusion: Women with a negative HPV test may safely be screened every 6 years.

STUDY

1. Seven primary screening studies included over 24 000 women (most over age 30). All routinely used both cytology and HPV tests. Included only women with adequate cytology and HPV tests at baseline, and with at least one follow-up cytological test.
2. Regarded abnormal cytology as the equivalent of atypical squamous cells of uncertain significance or worse.
3. Estimated the specific cumulative incidence rate of cervical cancer according to the original baseline groups; HPV + or - ; cytology + or -. Cytology tests in Europe are commonly recommended every 3 years.

RESULTS

1. Of the original 24 295 women, 381 developed confirmed cervical cancer during 6 years of follow-up.
2. Cumulative incidence of cervical cancer at 6 years (% per 10 000 subjects):

HPV + / cytology +	34	
HPV + / cytology -	10	
HPV - / cytology +	2.7	(ten patients)
HPV - / cytology -	0.27	(one patient)

3. The cumulative incidence of cancer in those HPV + rose continuously over 6 years. The cumulative rate of cancer in those positive for cytology & negative for HPV remained below 3%.

DISCUSSION

1. In patients negative for both tests, the cumulative incidence rate of future cancer during 6 years of follow-up was uniformly low. Double negativity confers a long lasting protective effect.
2. The long lasting protective effect was also low in women with positive cytology who were negative

for HPV.

3. Several other studies also reported low rates of cancer over long periods in women who were negative for both tests.
4. The HPV test results in more false positives (less specific) than cytology. There are fewer false positive tests for HPV in women over age 35. This suggests that restricting HPV testing to those over age 35 would reduce overdiagnosis. Predictive models should be based on CIN grade 3. Low and moderate grades of CIN often regress.

CONCLUSION

The consistently low 6-year cumulative incidence rate of cervical cancer among women with a negative HPV test suggests that screening intervals for HPV could safely be lengthened to 6 years. This could at least partially compensate for the increased referral rate resulting from the higher false positive rates of HPV-based screening strategies, especially in younger women.

BMJ October 28, 2008; 337: 969-72 Original investigation, first author Joakim Dilner, Lund University, Malmo, Sweden.

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Associated With Less Aggressive Medical Care And Earlier Referral To Hospice

10-3 ASSOCIATIONS BETWEEN END-OF-LIFE DISCUSSIONS, PATIENT MENTAL HEALTH, MEDICAL CARE NEAR DEATH, AND CAREGIVER BEREAVEMENT ADJUSTMENT.

End-of-life discussions (**EOLD**) offer patients the opportunity to define their goals and expectations for the medical care they want to receive near death. These discussions also mean confronting the limitations of medical treatments and the reality that life is finite, both of which may cause psychological distress. Talking about death can be difficult.

Patients with advanced cancer who prefer life-extending therapy are often overly optimistic about their chances of survival.

EOLD might reduce the aggressiveness of medical care near death by making patients more realistic about the benefits of intensive therapies.

This study examined the associations between EOLD and the medical care that terminally ill cancer patients receive. Do EOLD benefit or harm? Do they lead to fewer aggressive interventions?

Conclusion: EOLD were associated with less aggressive medical care and earlier referral to hospice.

STUDY

1. “Coping with Cancer” is a prospective, longitudinal cohort study of terminally ill cancer patients (n = 638) and their caregivers (spouse or adult child). It examines how psychosocial factors influence care of terminal patients and their caregiver’s bereavement adjustment.
2. All subjects had advanced cancer (presence of distant metastases and disease refractory to first-line chemotherapy), were over age 20, and had a presence of an informal caregiver. Followed patients for a median of 4 months.
3. This study (2002-08) was restricted to the 332 patients who died. It examined the medical care they received in the final week of life. The sample had disproportionately high rates of ethnic minorities who were highly symptomatic and had poor performance statuses.
4. Assessed caregiver’s psychiatric illness and quality-of-life at a median of 6 months later. (At a point that they would likely be beyond acute grief.)
5. At a baseline interview patients were asked “Have you and your doctor discussed any particular wishes you have about care you want to receive if you were dying?”
6. Recorded important predictors of end-of-life care: 1) patient’s treatment preferences, 2) advanced planning, 3) acknowledgement that their illness was terminal, 4) religiousness, 5) and patient-physician relationship.
7. Defined a close patient-physician relationship as one in which patients trusted and respected their physician, felt respected and “seen as a whole person”, and were very comfortable asking questions about their care.
8. Defined indicators of aggressive care: 1) admission to intensive care, 2) ventilation, 3) resuscitation, 4) chemotherapy, or 5) a feeding tube near death.

RESULTS

1. EOLD were not associated with patients being depressed, sad or worried. Patients did not meet criteria for any mental disorder.
2. Patients who engaged in the discussion were more likely to accept that their illness was terminal.
3. They were more likely to prefer treatment focused on pain and discomfort over life-extending therapies.
4. They were more likely to have completed a do-not-resuscitate order.
5. They received fewer aggressive interventions, were less likely to receive ventilation, undergo

resuscitation, and to be admitted to intensive care. They were more likely to be enrolled in hospice for more than a week. QOL improved the longer the patient enrolled in hospice.

6. Patients who received aggressive interventions had worse quality-of-life (**QOL**) in the final week. Their quality-of-life decreased with increasing aggressive treatment.
7. Bereavement outcomes: Caregivers of patients who received any aggressive care were at higher risk of developing a major depressive disorder, experiencing regret, and feeling unprepared for the patient's death. A direct relationship existed between patients' QOL near death and their bereaved caregivers' QOL at follow-up. Caregivers of patients with high quality-of-life felt better prepared for death and experienced less regret at follow-up.

DISCUSSION

1. EOLD may have cascading benefits for patient and their caregivers. There was no evidence that EOLD were associated with increased emotional distress or psychiatric disorders.
2. The worst outcomes were seen in patients who did not have these conversations. This group received more aggressive medical care in their final week of life and had worse QOL near death. Their bereaved caregivers experienced worse QOL, more regrets, and were at higher risk of developing a major depressive disorder 6 months later. Better patient QOL near death was associated with better QOL among caregivers.

3. Patients who received less than a week of hospice care had the same QOL scores as patients who received no hospice care, suggesting that patients benefit more from early hospice referral.
4. Recent studies have shown that communication interventions in intensive care units can reduce psychological distress among bereaved family members.

5 "We were further constrained by the limited information available on the discussions." "We do not know who initiated the conversation, when it happened, or what was said." EOLD are often poorly documented.

6. The association between EOLD and patients' preferences for less aggressive care is noteworthy. EOLD may make patients more realistic about benefits of aggressive therapies.
7. In this study, more than 60% of dying patients did not recall having an EOLD with their physicians. Physicians often avoid these conversations, are overly optimistic, and delay discussions until patients are close to death, perhaps because of their own feelings of failure or loss.
8. By acknowledging that death is near, patients, caregivers, and physicians can focus on

clarifying patients' priorities and improving pain and symptom management.

CONCLUSION

End-of-life discussions are associated with less aggressive medical care and earlier hospice referrals. Aggressive care is associated with worse quality-of-life and worse bereavement adjustment.

JAMA October 8, 2008; 300: 1665-73 Original investigation, first author Alexi A Wright, Dana Farber Cancer Institute, Boston Mass

Funded by the National Cancer Institute and the National Institute of Mental Health

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"A Strategy With Substantial Benefits"

10-4 EFFECTIVENESS OF MATERNAL INFLUENZA IMMUNIZATION IN MOTHERS AND INFANTS

Infants and pregnant women are at increased risk for serious consequences of influenza (eg, bacterial pneumonia and otitis media). Natural maternal influenza antibodies protect infants during the first months of life.

Inactivated flu vaccine is recommended for pregnant women, but is not licensed for infants younger than age 6 months. It is licensed for age 6 to 23 months. Anti-viral drugs for influenza are not licensed for infants under age 1 year.

Few pregnant women receive the vaccine.

This study assessed the clinical effectiveness of the inactivated vaccine administered during pregnancy.

Conclusion: Vaccine reduced illness in mothers and infants.

STUDY

1. Prospective, controlled, blinded study in Bangladesh randomized 340 women in the 3rd trimester of pregnancy to: 1) inactivated influenza vaccine, or 2) pneumococcal vaccine (control group). All infants also received either pneumococcal conjugate vaccine or Hib conjugate vaccine.
2. Primary outcome in infants was the first episode of laboratory-confirmed influenza before age 24 weeks.

RESULTS

1. Over a 17-month follow-up:

	Laboratory-confirmed influenza
Infants of vaccinated mothers (n = 172)	6 cases
Infants of mothers not vaccinated (n = 168)	16 cases
(Vaccine effectiveness for infants was 63%)	
	Respiratory illness with fever
Infants of vaccinated mothers (n = 172)	110 cases
Infants of mothers not vaccinated (n = 168)	153 cases
(Vaccine effectiveness 29%)	

2. Among mothers, there was a reduction in the rate of respiratory illness with fever of 36% compared with non-vaccinated.
3. Clinical effectiveness in infants lasted up to 6 months of age.

DISCUSSION

1. In subtropical and tropical regions, influenza viruses may circulate and cause disease for much of the year.
2. "Our data show that a single dose of maternal influenza vaccine provides a considerable two-for-one benefit to both mothers and their young infants."
3. The absolute reduction in the rate of illness showed that every 100 immunizations prevented respiratory illness with fever in 14 infants and 7 mothers. Five mothers would have to be vaccinated to prevent a single case of respiratory illness with fever in a mother or infant.

CONCLUSION

Inactivated influenza vaccine reduced proven influenza illness by 63% in infants up to 6 months of age and averted approximately a third of all febrile respiratory illnesses in mothers and young infants.

Maternal influenza immunization is a strategy with substantial benefits.

NEJM October 9, 2008; 359: 1555-64 Original investigation, first author K Zaman, International Centre for Diarrheal Disease Research, Dhaka, Bangladesh.

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Metformin Moderately Protective; Rosiglitazone Possibly Harmful.

10-5 CARDIOVASCULAR OUTCOMES IN TRIALS OF ORAL DIABETES MEDICATIONS

A wide variety of oral diabetes medications is currently available. It is not clear how these agents compare with respect to long-term cardiovascular risk. Most clinical trials focus on intermediate outcomes such as HbA1c, lipids, and blood pressure.

Improvements in control of glucose levels have been shown to reduce incidence of *micro*vascular disease.

This systematic review asks how the different oral drugs affect hard clinical outcomes, including cardiovascular morbidity and mortality and all-cause mortality.

Conclusion: Compared with other agents and placebo, metformin was moderately protective against cardiovascular outcomes. Rosiglitazone was possibly harmful.

STUDY

1. A literature search found 40 randomized controlled trials that reported *macro*vascular outcomes and mortality associated with second-generation sulfonylureas, biguanides, thiazolidinediones, and meglitinides for treatment of type-2 diabetes (**DM-2**).
2. Evaluated risk of fatal and non-fatal cardiovascular disease (**CVD**) and all-cause mortality. (Most of the trials, however, were not powered to examine cardiovascular events.)

RESULTS

1. Metformin[1] vs placebo or other oral agents for cardiovascular mortality (7 trials)
   Overall pooled odds ratio = 0.85 favoring metformin.(CI = 0.68 to 1.05)
   The only statistically significant trial was UKPDS 34—odds ratio = 0.58 (CI = 0.40 to 0.84)
2. Any sulfonylurea vs placebo or other oral agent (5 trials)
   Overall pooled odds ratio = 0.89 favonian sulfonylurea (CI = 0.69 to 1.11)
3. Rosiglitazone[2] vs placebo or other oral agents (5 trials)
   Overall pooled odds ratio = 1.69 favonian placebo or other agents (CI = 0.51 to 6.11)
4. Pioglitazone vs placebo or other oral agents (6 trials)
   Overall pooled odds ratio = o.86 favonian pioglitazone (CI = 0.78 to 1.00)

DISCUSSION

1. Metformin was the only drug associated with a significant *decrease* in mortality.
2. Rosiglitazone was the only drug associated with a possible *increase* in risk of cardiovascular

morbidity or mortality, but these results were not statistically significant.

3. "The poor quality and inconsistent reporting of adverse events and the profound lack of long-term studies make it difficult to draw firm conclusions."
4. Glycemic control per se may be partially driving cardiovascular risk reduction.
5. "The current evidence based on comparison of specific oral diabetes medications for the risk of cardiovascular morbidity and mortality is inconclusive."

CONCLUSION

Compared with other oral agents, metformin appears moderately protective against cardiovascular effects and rosiglitazone is possibly harmful.

A lack of power prohibits firm conclusions.

Archives Int Med October 27, 2008; 168: 2070-80 Review article, a systematic review, first author Elizabeth Selvin, Johns Hopkins Bloomberg School of Public Health, Baltimore MD

1 Metformin is now available generically. Some pharmacies sell 1000 mg #100 for $10. This augments the benefit/harm-cost ratio. No drug company will underwrite costs of a large randomized trial to assess its cardiovascular benefits.

2 The American Diabetes Association has issued guidelines that explicitly advise against use of rosiglitazone for type-2 diabetes.

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Increases In Levels Of Insulin, Not Glucose, May Be Etiologic

10-6 GLUCOSE LOWERING TO CONTROL MACROVASCULAR DISEASE IN TYPE-2 DIABETES

Intensive glycemic control for type-1 diabetes reduces risk of developing *micro*vascular complications (neuropathy, retinopathy and diabetic kidney disease). "Indeed, for patients with type-1 diabetes, aggressive insulin treatment also reduced the long-term risk of cardiovascular disease."

Therapeutic enthusiasm for intensive treatment expanded to include patients with type-2 diabetes (**DM-2**) who have insulin resistance, rather than the absence of insulin production, which is characteristic of type-1 diabetes.

"Elevated glucose levels in patients with type-2 diabetes, like the high white blood cell counts in patients with bacterial pneumonia, are a consequence of insulin resistance, together with inadequate compensatory hyperinsulinemia."

Improved glycemic control in DM-2 is associated with prevention of *micro*vascular complications.

Numerous trials have demonstrated that high levels of HbA1c and glucose are predictors of cardiovascular disease. The relationship of glucose levels to cardiovascular disease mortality is especially strong in patients with established cardiovascular disease.

Whether reduction of cardiovascular risk would result from intensive glycemic control in DM-2 remains an unanswered hypothesis. A recent large trial[1] of intensive treatment of DM-2 was stopped early because of an increase in total mortality. Other trials have failed to provide evidence that intensive glucose control leads to cardiovascular protection.

The paradox may perhaps be explained by insulin resistance or hyperinsulinemia. In large population-based studies, insulin levels predicted increased cardiovascular risk. High fasting insulin concentrations have been reported to be an independent predictor of ischemic heart disease. This raises the possibility that increases in levels of insulin, not glucose, may be etiologic in cardiovascular disease. Insulin has mitogenic effects on vascular smooth muscle and increases activity of plasminogen activator inhibitor, thereby decreasing fibrinolytic activity.

"If insulin levels are toxic to the cardiovascular system, then treatments designed to reduce insulin levels, rather than glucose levels, might be associated with a reduced risk of cardiovascular events in patients with type-2 diabetes."

Some prior clinical trials support the idea that therapies to lower insulin levels may be effective in preventing *macro*vascular disease.

Metformin, in addition to reducing glucose levels, also reduces insulin levels. Relative to insulin and sulfonylureas, which increase plasma insulin levels, metformin has been associated with a long-term reduction in risk of myocardial infarction

"It may be appropriate to focus also on the aggressive control of insulin levels or insulin resistance rather than only on aggressive control of glucose levels."

"For the prevention of cardiovascular disease in patients with type-2 diabetes, intensive treatment of glucose levels may resemble aggressive efforts to reduce white blood cell counts in patents with bacterial pneumonia."

JAMA November 5, 2008; 300: 2051-53 "Commentary", first author Mark O Goodarzi, David Gelfin School of Medicine, UCLA, Los Angeles, CA

1 The ACCORD trial NEJM 2008 ; 358: 2560-72

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Similar Glycemic Control Occurred With NPL or IG When Added To Oral Regimens

10-7 ADDITION OF NEUTRAL PROTAMINE INSULIN LISPRO OR INSULIN GLARGINE TO ORAL TYPE-2 DIABETES REGIMENS FOR PATIENTS WITH SUBOPTIMAL GLYCEMIC CONTROL

Glycemic control, preferably to HbA1c levels less than 7%, can substantially reduce the risk of *micro*vascular, and possibly *macro*vascular complications in patients with type-2 diabetes (**DM-2**). Maintaining such levels is now recommended for clinical practice, but it is difficult to achieve despite escalating doses of oral drugs.

Secondary failure (HbA1c > 7%) occurs in 40% to 60% of patients after a few years of treatment with oral drugs. Most patients with DM-2 eventually require insulin added to oral agents as glycemic control becomes suboptimal. A single bedtime injection of a long-acting insulin added to oral agents is then the preferred treatment worldwide.

The basal insulin analogue glargine (**IG**) has a long duration of action (about 24 hours) with no discernable peak in circulating insulin concentration.

Neutral protamine lispro (**NPL**) is a protamine based, intermediate acting insulin formulation of insulin lispro. Onset of action is 1 to 4 hours after injection, a peak at 6 hours, and a duration of about 15 hours.

This study compared the clinical efficacy and safety of bedtime NPL and IG added to ongoing oral therapy with stable doses of metformin and sulfonylureas in patients with DM-2. All had suboptimal control. Oral agents were continued at the pre-study doses. But, only metformin was permitted at the evening meal in order to minimize risk of sulfonylurea-induced nocturnal hypoglycemia.

Conclusion: Similar glycemic control occurred with NPL and IG when added to oral regimens in poorly controlled patients with DM-2.

STUDY

1. This open-label randomized trial compared the clinical efficacy and safety of NPL or IG when added to oral therapy in patients with DM-2 poorly controlled with oral therapy alone.
2. Followed 116 adults who were receiving stable doses of metformin + sulfonylureas for longer than 90 days. All had HbA1c levels 7.5% to 10% and fasting plasma glucose levels $\underline{\geq}$ 120 mg/dL.
3. Mean levels at baseline

   Age = 54; BMI = 29; HbA1c = 8.8%; fasting blood glucose = 192 mg/dL
4. Randomized to 10 IU of NPL (*Humalog NPL*; Lilly) or IG (*Lantus*; Sanofi-Aventis) at bedtime. Adjusted dose of insulin to target fasting glucose less than 100 mg/dL.

5. Primary efficacy assessment was the change in HbA1c from baseline to end of follow-up at week 36.

RESULTS

1. HbA1c improved equally in both groups (- 1.8%), reaching a plateau after 12 to 24 weeks.
2. Secondary outcomes did not differ between groups: HbA1c levels below 7% (62%); fasting plasma glucose < 100 mg/dL (40%); insulin dose; and body weight.
3. Mean FPG at end of follow-up was 106 mg/dL.
4. Insulin dose at end of study was 52 IU for IG and 57 IU for NPL.
5. Weight increased in both groups: + 2.4 kg with NPL and + 2.8 kg for IG.
6. Hypoglycemia:

	NPL	IG	
Any hypoglycemic event:	74%	67%	(About 7 to 6 episodes per year per patient)
Symptomatic hypoglycemia	45%	40%	
Nocturnal hypoglycemia	33%	25%	
Severe hypoglycemia	0	0	

DISCUSSION

1. Combination therapy with oral drugs during the day and intermediate-acting insulin at bedtime has proven to be an effective and feasible therapeutic approach.
2. The risk for nocturnal hypoglycemia associated with aggressive therapy may limit the dose of bedtime insulin.
3. “The results of our study confirm the feasibility of adding basal insulin to oral antihyperglycemic drugs, with intensive dose titration as a strategy for achieving recommended glycemic targets in patients with poorly controlled type-2 diabetes.”
6. Tight glycemic control increases the risk for hypoglycemia. This is a major barrier to sustained control.
7. The use of evening metformin (instead of combined metformin-sulfonylurea) might have smoothed stimulation of endogenous insulin during the night.
8. The authors comment that the old Neutral Protamine Hagedorn (NPH) insulin exhibits a peak at 4 to 6 hours after injection with a duration of action of about 12 hours. It costs 1/3 less than IG. Studies comparing IG with NPH have consistently found similar overall glycemic control, but less hypoglycemia with IG.

CONCLUSION

Bedtime IG or NPL added to oral medication in patients with poorly controlled DM-2 resulted in similar glycemic control. Hypoglycemia was similar in the two groups, but the sample size limited the ability to make a definite safety assessment.

Annals Int Med October 21, 2008; 149: 531-39 Original investigation, first author Katherine Esposito, Second University of Naples and Azienda Sanitaria, Naples, Italy
Supported in part by the Second University.

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A Legacy Effect

10-8 10-YEAR FOLLOW-UP OF INTENSIVE GLUCOSE CONTROL IN TYPE-2 DIABETES

The United Kingdom Prospective Diabetes Study (UKPDS; 1998)[1] reported that patients with type-2 diabetes (**DM-2**) who received intensive glucose-lowering therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy. And a non-significant reduction in myocardial infarction. In overweight patients who primarily took metformin[2], the risk of myocardial infarction (**MI**) was reduced by a significant 39%. Risk of death from any cause was reduced by 36%.

This 10-year post intervention study (after the between-group differences in HbA1c were lost) followed UKPDS survivors to determine if there were continued microvascular and macrovascular benefits.

Conclusion: There was a continued reduction in microvascular risk and risk reductions for MI and death from any cause.

STUDY

1. The original UKPDS enrolled patients from 1977 to 1991, and was reported in 1998. At baseline, over 4200 patients with newly diagnosed DM-2 were randomized to: 1) dietary restriction, or 2) intensive therapy with sulfonylurea-insulin, or to 3) metformin (in overweight patients).
2. This post-trial study monitored over 3200 of the trial patients for an additional 10 years (1998-2007). No attempt was made to maintain their previously assigned therapy.
3. Examined clinical outcomes on an intention-to-treat basis, according to the previous randomization categories.

RESULTS

1. Between-group differences in Hba1c were lost after the first post-trial year.

2. Outcomes at 2007:

A. Sulfonylurea + insulin group	Absolute risk (per 1000 patient-years)	
	Intensive therapy	Conventional therapy
Any diabetes-related end-point	48	52
Diabetes-related death	15	17
Death from any cause	27	30
Myocardial infarction	17	20
Stroke	6.3	6.9
Peripheral vascular disease	2.0	2.4
Microvascular disease	11	14
B. Metformin group		
Any diabetes-related end-point	46	54
Diabetes-related death	14	19
Death from any cause	26	33
Myocardial infarction	15	21
Stroke	6.0	6.8
Peripheral vascular disease	2	3
Microvascular disease	12	13

3. In the sulfonylurea-insulin group, in 2007, as compared with dietary restriction, statistically significant relative risk reductions persisted: any diabetes-related end point (9%); diabetes-related death (17%); myocardial infarction (15%); death from any cause (13%); and microvascular disease (24%), There were no significant risk reductions in stroke or peripheral vascular disease.

4. In the metformin group, in 2007, as compared with the dietary restriction group, statistically significant relative risk reductions persisted for any diabetes-related end point (21%), diabetes-related death (30%); MI (33%), and death from any cause (27%). There were no significant reductions in microvascular disease, stroke, or peripheral vascular disease.

DISCUSSION

1. “This large post-trial study showed that benefits of an intensive strategy to control blood glucose levels in patients with type-2 diabetes were sustained for up to 10 years after cessation of randomized interventions.”

2. The benefits persisted despite the early loss of differences in glycated hemoglobin levels between the intensive-therapy group and the conventional group—a so called legacy effect.
3. There were also differences in outcomes between an intensive glucose-control strategy using sulfonylurea-insulin, and a strategy using metformin (in overweight patients).
   A. In the sulfonylurea-insulin group, the significant reduction of 25% in the risk of microvascular disease was sustained during the post-trial period, despite a similar convergence of glycated hemoglobin in the sulfonylurea-insulin and diet-alone groups
   B. In the metformin group, throughout the post-trial period, substantial risk reductions occurred for MI (39%), and death from any cause (36%) despite a similar convergence of glycated hemoglobin in the metformin and diet-alone groups
4. The pathophysiological mechanisms for the legacy effect of intensive glycemic control are unclear. Long-term hyperglycemia is associated with a slow onset of microvascular disease, which may be mediated by the gradual accumulation of advanced glycation end-products that are subsequently slowly degraded with intensive glycemic control. This mechanism could also be implicated in development of cardiovascular disease.
5. “Our results show a sustained legacy effect of an intensive glucose-control strategy that appears to be longer than previously reported.”
6. Intensive glucose control starting at the time of diagnosis is associated with a significantly decreased risk of myocardial infarction and death from any cause, in addition to the well-established reduction in the risk of microvascular disease.

CONCLUSION

Despite early loss of glycemic differences, a continued reduction in microvascular risk and myocardial infarction and death from any cause was observed during 10-years of post-trial follow-up.

NEJM October 9, 2008; 359: 1577-89 Original investigation, first author Rury R Holman, Oxford Centre for Diabetes, Endocrinology, and Metabolism, Oxford UK.

1 Lancet 1998; 354: 837-53 (See Practical Pointers September 1998)

2 Lancet 1998; 354: 854-65 (See Practical Pointers September 1998)

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A Promising Treatment Option

10-9 EXENATIDE ONCE WEEKLY VERSUS TWICE DAILY FOR THE TREATMENT OF TYPE-2 DIABETES

Incretins are hormones normally produced by the upper gastrointestinal tract after eating, even before the blood glucose rises They have multiple glucoregulatory effects: enhancement of glucose-dependent insulin secretion, reduction of glucagon secretion, reduction of food intake, and slowing of gastric emptying. As a result, plasma glucose levels are reduced.

Glucagon-like-peptide-1 (**GLP-1**) fulfills the criteria for an incretin. It is rapidly inactivated by a peptidase. It is not clinically useful. It must be administered by continuous subcutaneous infusion.

Two new classes of antidiabetes agents have been approved for treatment of type-2 diabetes (**DM-2**) They potentate the action of incretins.

1) Incretin mimetics: glucagon-like peptide receptor agonists (GLP-1 receptor agonists; eg, exenatide (*Byetta*; Amylin; Lilly).
2) Incretin enhancers: eg, sitagliptin (*Januvia*; Merck) inhibit the peptidase which degrades incretins. May be given orally.

Exenatide is a GLP-1 analogue (an incretin mimetic), a 39-amino-acid peptide bearing a 50% amino-acid homology to GLP-1. It displays biological properties similar to human GLP-1. Its half life is over 2 hours. It is produced by chemical synthesis.

Exenatide significantly improves glycemic control in patients suboptimally controlled by commonly used oral agents including metformin, sulfonylureas, and thiazolidinediones. The exenatide currently available requires twice daily subcutaneous injections. It does not provide continuous activation of receptors.

A long-acting form of exenatide has been developed for once-weekly injection. The sustained-release formulation (SRF-exenatide**; SRFE**) consists of microspheres of exenatide combined with a common biodegradable medical polymer, which has established use in absorbable sutures and extended release pharmaceuticals. This allows gradual drug delivery in a controlled rate.

This study compared safety and efficacy of the SRFE given once-weekly with that of the older preparation given twice daily in patients with DM-2.

Conclusion: SRFE once weekly resulted in greater improvements in glycemic control with no increased risk of hypoglycemia.

STUDY

1. A 30-week open-label randomized, non-inferiority study entered 295 patients with DM-2. It

compared: 1) the long-acting SRFE 2 mg given once-weekly, with 2) short-acting exenatide starting at 10 ug given twice daily. The drugs were self-administered. All patients were weight stable.

2. At baseline (means):

HbA1c	8.3%
Age	55
Fasting glucose	162 mg/dL
BMI	35
Weight	102 Kg
Duration of DM-2	7 years.

3. All were being treated with diet modification and exercise. All were receiving metformin, a sulfonylurea, a thiazolidinedione, or any combination of two of these, or were naïve to oral drugs. Patients on a sulfonylurea had their evening dose reduced in order to reduce risk of hypoglycemia.
4. The oral drugs were continued.
5. Primary endpoint = change in HbA1c at 20 weeks.

RESULTS

1. In patients treated once-weekly, mean plasma levels of exenatide increased progressively and reached a plateau between 6 and 10 weeks.

2. Outcomes at 30 weeks (mean):	SRFE	Twice daily
Reductions in HbA1c	1.9%	1.5%
HbA1c 7% or less	77%	61%
Fasting glucose mg/dL	- 41 mg/dL	- 25 mg/dL
Weight loss	- 3.6%	- 3.7%

Postprandial plasma glucose and glucagon levels were lower in the SRFE group.

3. More than 75% of patients in both groups lost weight.
4. Changes from baseline in cardiovascular parameters:

	Once a week	Twice daily
Triglycerides	- 15%	-11%
Total cholesterol (mg/dL)	-12	- 4
HDL-cholesterol (mg/dL)	-1	-1
LDL-cholesterol(mg/dl)	-5	+1

6. Both systolic and diastolic BP declined in both groups by about 4/1.7 mm Hg.
7. Anti-exenatide antibodies developed in some patients. At study end, 4 patients had antibody titers of

1/3125—3 in the weekly and 1 in the twice daily. Of these, one had a reduction in HbA1c, 2 had an increase; one had no change. Two had an increase in weight; one had no change.

8. Gastric emptying measured by serum levels of orally acetaminophen showed a greater slowing—more so in the weekly group.
9. Adverse effects:

    Nausea was common (34%); vomiting (18%), predominantly mild.

    No episodes on major hypoglycemia, irrespective of background sulfonylurea use.

    Withdrawals due to adverse events were 6.1% for once weekly and 4.8% for twice daily.
10. Patients in the once weekly group reported an increase in treatment satisfaction.

DISCUSSION

1. A greater reduction in HbA1c was observed in the once-weekly group (1.9%) than in the twice daily group (1.5%). This was likely due to the continuous exposure to exenatide resulting in a greater suppression of fasting glucose.
2. Both treatments were generally well-tolerated. Nearly 90% of the once weekly group completed the 30 week study.
3. Although antibodies developed in both groups, and were higher in the once-weekly group, the presence of antibodies did not correlate with rates of reported adverse events. Most patients with measurable antibodies at the end of the study had significant reductions in HbA1c.
4. Continuous treatment offers a promising treatment option for management of DM-2.

CONCLUSION

Exenatide once-weekly resulted in greater improvements in glycemic control than exenatide given twice daily, with no increase in risk of hypoglycemia and with similar reductions in body weight.

Lancet October 4, 2008; 372: 1240-50 Original investigation, first author Daniel J Drucker University of Toronto, Canada**.**

Study was funded by Lilly and Amylin

Incretins do not increase insulin levels. (Personal communication Amylin Corp.)

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Currently Imperfect, But Promising

10-10 STOOL DNA AND COLON CANCER PREVENTION

Despite the recognition that colo-rectal cancer (**CRC)** is largely preventable, it remains the second leading cause of cancer death in the US.

Historically, screening approaches have sought to detect established cancer. The identification of precancerous adenomatous polyps is clearly preferable.

Not all adenomas progress to cancer. Those that are larger than 1 cm that contain villous histology or high grade dysplasia are likely to do so.

Guidelines now emphasize detection of precancerous polyps as the most effective strategy to prevent death from CRC. Colonoscopy is recommended. Testing for occult blood in the stool is notoriously insensitive.

The adenoma-to-carcinoma sequence in colon cancer is based on the stepwise progression of specific genetic alterations that parallel the histopathologic progression from pre-neoplasia to neoplasia. Detection of gene mutations in tumor cells sloughed off into stool is possible. Two DNA tests are available—Stool DNA Test-1 (**SDT-1**) and more recently **STD-2.** The latter assay includes 3 genes which are classically mutated at the stage of precancerous adenomas. (The tests are expensive.)

An article in this issue of Annals[1] evaluated DNA tests in a screened population of over 3300 adults. It compared the sensitivity and specificity of the DNA tests with occult blood for the diagnosis of screen relevant neoplasms (adenoma larger than 10 cm with high-grade dysplasia, and potentially curable CRC).

STD-1 had 20% true positives; 80% false negatives (sensitivity = 20%) for screen-relevant neoplasms. Hemoccult had a sensitivity of 16%; Hemoccult Sensa 24% . Sensitivity of SDT-1 for detection of invasive cancer was 25%.

STD-2 was much more promising—46% of screen relevant neoplasms had a positive result. (Sensitivity = 46%) This would miss more than half of screen-relevant neoplasms. There were many false positives—16% to 26% of those tested positive did not have a neoplasm. Such high false positive rates would be problematic for population-wide screening.

Stool DNA testing is currently imperfect. Technological advances will come primarily in the form of more sensitive polymerase chain reaction strategies.

For those unwilling to have a screening colonoscopy, a stool DNA could provide a noninvasive option that is superior to conventional occult blood testing.

Annals Int Med October 7, 2008; 149: 509-10 Editorial by David C Chung, Massachusetts General Hospital, Boston Mass

1 "Stool DNA Testing and Occult Blood Testing in Screen Detection of Colorectal Neoplasia" Annals Int Med October 7, 2008; 149: 441-450 Original investigation, first author David A Ahlquist, Mayo Clinic, Rochester, Minn.

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10-11 WHAT HAPPENED TO THE POLYPILL?

In 2003[1] , Wald and Law published an article describing a "polypill" which they stated would reduce incidence of heart attacks and stroke by 80%. The pill was to be taken by everyone over the age of 55 without pre-testing or follow-up . It contained aspirin, a statin, a diuretic, a beta-blocker, an ACE inhibitor, and folic acid—all generics and at low dose. The logic was that most people in Western society are at increased risk of cardiovascular disease, and that the drugs are effective and safe. Each component has been used for years with substantial evidence of safety. The authors suggested the pill would reduce incidence of stroke and heart attacks by 80%, and add an additional 11 years of life free of ischemic stroke and myocardial infarction to the general population.

It was termed "One of the boldest claims for a new intervention."

Adverse effects would occur in about 15% of persons. Aspirin would cause the most.(bleeding). Beta-blocker is not suitable for persons with asthma. Statins may cause muscle problems. The benefits would outweigh the risks.

Now, more than 5 years later, you might imagine that research groups would be competing to test this innovative suggestion. Not so. The few trials that have been planned lack the scope and ambition of the original proposal. Some small trials have been limited to secondary prevention.

Some authorities have objected because they feel this is not the solution for primary prevention. They would limit the pill to secondary prevention. "Primary prevention requires education of the public. As a priority this is much more important than the polypill" Wald replies that, in an ideal world, saturated fat intake would be lower, we would exercise more, use less salt and sugar in our diet. But, this is not going to happen. And, why would lifestyle and the polypill be mutually exclusive?

The polypill concept is also accused of medicalizing the population. Wald argues that if you test people to see if they have high BP or high cholesterol, they are given a disease label and must come back regularly to recheck. "You have created a patient." This is real medicalization—not universal access to a pill.

Does he sense a moral objection to use of the pill? He responds: “Is getting a vaccination a moral weakness?”

BMJ October 4, 2008; 337: 786 Commentary, “Preventive Medicine, by Geoff Watts freelance journalist, London UK

1 BMJ 2003; 326: 1419-24 See Practical Pointers June 2003 [6-1] *I abstracted some of the comments from the original article.*

2 Folate was subsequently omitted because additional studies reported it is ineffective. The folate-homocysteine-cardiovascular risk connection has been disproved

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