

**PRACTICAL POINTERS**  
**FOR**  
**PRIMARY CARE**  
**ABSTRACTED MONTHLY FROM THE JOURNALS**  
**SEPTEMBER 2007**

**METFORMIN AND SULFONYLUREAS ARE PREFERRED ORAL DRUGS FOR TYPE-2 DIABETES**

**HbA1c IS NOT THE MOST IMPORTANT RISK FACTOR IN PATIENTS WITH TYPE-2 DIABETES**

**ATTEMPTING TO ATTAIN MINIMUM-EFFECTIVE DOSES OF LONG-TERM DRUGS**

**NOROVIRUSES—AN INCREASING THREAT TO COMMUNITY HEALTH**

**MUST HOSPICE PATIENTS GIVE UP AGGRESSIVE TREATMENTS?**

**HOSPITALS EMBRACE PALLIATIVE CARE**

**AN EXEMPLARY HOSPICE COMBINES PALLIATIVE CARE WITH HOSPICE CARE**

**MORE EVIDENCE THAT HIGH TRIGLYCERIDE LEVELS INCREASE RISK OF CHD**

**TRIGLYCERIDES AND CORONARY HEART DISEASE, REVISITED**

**A PLEA FOR GREATER UNDERSTANDING BETWEEN SCIENCE AND THE GENERAL PUBLIC.**

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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.

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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 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](http://www.practicalpointers.org)

Richard T. James Jr. M.D.

Editor/Publisher.

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# HIGHLIGHTS AND EDITORIAL COMMENTS SEPTEMBER 2007

## *Metformin and Sulfonylureas Win the Day*

### 9-1 COMPARATIVE EFFECTIVENESS AND SAFETY OF ORAL MEDICATIONS FOR TYPE 2 DIABETES A Systematic Review

As newer oral agents are increasingly marketed for treatment of type-2 diabetes (DM2), clinicians and patients must decide whether they prefer these generally more costly medications (eg, thiazolidinediones; meglitinides) or the older agents (metformin; sulfonylureas).

This study summarized the benefits and harms of oral agents used in treatment of DM2:

2<sup>nd</sup> generation sulfonylureas (All 3 are generic)

- a. glyburide (formerly *Micronase*; *Diabeta*)
- b. glipizide (formerly *Glucotrol*)
- c. glimepiride (*Amaryl*)

Metformin (a biguanide; Generic; formerly *Glucophage*)

Thiazolidinediones (eg, rosiglitazone [*Avianda*] and pioglitazone [*Actos*])

Meglitinides (repaglinide [*Prandin*] and nateglinide [*Starlix*])

Alpha-glucosidase inhibitor (acarbose; *Precose*)

Heretofore, no systematic review has summarized all available head-to-head comparisons with regard to the full range of intermediate endpoints (HbA1c, lipids, and body weight), and other clinically important outcomes such as adverse effects and macro-vascular risks. (Several studies of treatment of DM2 have suggested that improved glycemic control reduces micro-vascular events. In contrast, the effects of treatment of macro-vascular events are more controversial.)

This review found that evidence was inconclusive regarding major clinical endpoints (all cause mortality; cardiovascular mortality, non-fatal MI and stroke, as well as micro-vascular outcomes).

This review therefore was limited to intermediate endpoints—HbA1c; bodyweight; BP; lipids, and major adverse effects, including hypoglycemia.

When used as monotherapy, thiazolidinediones, sulfonylureas, repaglinide, and metformin were associated with about a 1% reduction in HbA1c. Various combinations of metformin + sulfonylurea; metformin + thiazolidinediones; sulfonylurea + thiazolidinediones have additive effects—another 1% reduction compared with monotherapy.

For all intermediate endpoints, metformin was similar to, or better than, other currently available oral agents. Overall, metformin seemed to have the best benefit / harm ratio. (*And a higher benefit / cost ratio. RTJ*) Second-generation sulfonylureas also fared well against other agents apart from the increased risk of hypoglycemia.

Conclusion: Compared with the newer, more expensive agents, metformin and second-generation sulfonylureas have similar or superior effects on glycemic control, lipids, and other intermediate endpoints.

These findings support the current American Diabetes Foundation recommendations that favor metformin as initial oral pharmacotherapy for DM2.

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*This is a work in progress. It is a preliminary report, not the last word. Debate will continue.*

*Recommendations by systematic reviews and guidelines must be updated periodically.*

*The incretin agents were not included. More dual (combined) tablets are becoming available*

*If oral therapy results in good HbA1c control, I believe it likely that there would be benefits in reducing micro-vascular events (retinopathy, neuropathy,, and nephropathy). The authors seemed to hedge on this point. Regarding macro-vascular outcomes, if metformin is related to a lowering of LDL-cholesterol, to maintenance of weight, and to a lower triglyceride level, it seems to me that this should translate into a lower risk of cardiovascular disease.*

*Should we encourage patients who are well controlled on oral medications other than metformin and sulfonylureas to switch? Unless the patient was stressed by cost of other drugs, I would not. If the patient was satisfied and well-controlled with present therapy, I would let well-enough alone. I would be reluctant to put him or her through a changing program.*

*Glucose control (determined by HbA1c) is not the most important factor determining outcomes in patients with DM2. See the following abstract.*

### ***“The Apparent Benefits Of Surrogate Outcomes Are A Mirage”***

#### **9-2 PATIENT-IMPORTANT OUTCOMES IN DIABETES—Time For Consensus**

Diabetes trials have focused on the effects of interventions on glucose control (HbA1c levels) rather than on patient-important outcomes. Measurement of HbA1c purportedly captures the effect of therapy on diabetes complications—the lower the HbA1c, the lower the risk of complications. The Diabetes Control and Complications Trial offered the best evidence to support this putative link. In patients with type 1 diabetes, DCCT established that near-physiological replacement of insulin lowered HbA1c concentrations and reduced the risk of micro-vascular complications (retinopathy, nephropathy, and neuropathy). And with less certainty, reduced risk of macro-vascular complications.

Unfortunately, HbA1c loses its validity as a surrogate marker when patients have a constellation of metabolic abnormalities, when the most important common complications are macro-vascular. This situation characterizes DM2.

The history of medical therapeutics is littered with instances in which reliance on surrogate outcomes has provided misleading results. Despite these lessons, trialists continue to rely on surrogate outcomes to substitute for patient-important outcomes. The apparent benefits of surrogate outcomes are a mirage.

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*We must stress treatment of all risk factors for complications of DM2—a global approach.*

*I can immediately count at least seven risk factors in addition to HbA1c which may require treatment in patients with DM2. Some are amenable to lifestyle changes only. Some can be reduced by drug therapy, I believe we should reduce these risk factors even if they are in the high normal range, and not wait until they pass some arbitrary “normal range”.*

*This does not mean that lowering HbA1c levels is unimportant. I believe it is established that obtaining consistently normal levels will reduce risk of micro-vascular complications.*

### ***Guiding Individual Patients in Their Pursuit of Dose Minimization***

#### **9-3 CAN DRUG REGIMENS BE ADAPTED TO PATIENTS, OR VICE VERSA?**

This commentary starts with a recognition that drug non-adherence is often intentional. Many people change their regimens because they have concerns about their drugs. Besides stopping medications altogether, patients may start to take drugs symptomatically or strategically, adjust dose to reduce unwanted consequences, or make regimens more socially acceptable. Such modifications show a desire to keep drug use to a minimum. This is sometimes evident by supplementation or replacement of a drug treatment with non-drug measures, or non-conventional remedies.

Prescribers not only need good communication skills for pursuing concordance, but could also benefit from evidence about the potential advantages and risks of guiding individual patients in their pursuit of dose minimization instead of always attempting to enforce compliance.

Minimum effective doses can vary with individual differences in body weight, organ functions, and pharmacogenetic properties. Dose recommendations in package inserts and textbooks have often been derived from pivotal clinical trials that were not designed to establish minimum effective doses in individuals. Lower daily doses and taking the prescribed drug less often than every day may be just as effective, and associated with fewer adverse effects.

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*Even the most conscientious patients are not 100% compliant. In well monitored trials, if pill counts report that subjects take as little as 80% of their assigned drug dose, they are considered well-compliant.*

*I am convinced that many patients, especially elders are over-medicated. They are prescribed too large continuing doses as well as too many different drugs. Many prescribers depend blindly on the PDR recommended doses, especially for older patients whose kidney and liver functions are impaired.*

*I believe an important rule for long-term medication is to start low and go slow. This applies mainly to long-term risk-reduction medications (eg anti-hypertension drugs, lipid-control drugs, anti-diabetes drugs). Short-term drugs (eg, antibiotics) must be prescribed as the recommended doses. If a second drug is added to improve long-term outcome, I believe reducing doses of both drugs at outset, and then gradually increasing doses, is a prudent approach.*

*Self-monitoring, (as with hypertension) is basic of effectiveness of dose reduction.*

*Reducing dose (especially when aided with a pill-cutter) may lead to considerable cost savings.*

***“The Most Common Cause Of Non-Bacterial Gastroenteritis”***

**9-4 NOROVIRUSES—CHALLENGES TO CONTROL**

This is a novel group of RNA viruses originally referred to as Norwalk-like agents—named after Norwalk Ohio, where an outbreak of illness was caused by the prototype agent—now called noroviruses.

There is no satisfactory animal model for norovirus disease. This hampers progress of vaccine development.

The characteristics and pathogenesis of noroviruses have been elucidated largely through studies of disease in humans and molecular analysis of virus from human stool samples. Several techniques can detect virus in the stools.

With increased ability to detect the virus, noroviruses are now recognized as the most common cause of non-bacterial gastroenteritis.

The illness usually entails both vomiting and diarrhea (4 to 8 non-bloody stools daily), often accompanied by nausea, abdominal cramps, and systemic symptoms. Fever (usually low grade) is present in about half the cases. Manifestations usually last one to three days. They are usually mild and self-limiting. But, at the height of the illness, symptoms may be incapacitating.

Infection may be spread person-to-person, or be waterborne or foodborne. Foodborne transmission has been particularly prominent (up to 50% of outbreaks).

Noroviruses are extremely infectious. As few as 10 particles may be needed to cause infection. They are highly resistant to inactivation by freezing, heating to 60<sup>0</sup> C, exposure to chlorine in concentrations of 1.0 mg/liter, pH levels of 2.7, and treatment with ether, ethanol, and detergent-based cleaners.

The primary control measures are environmental decontamination, prevention of contamination of water and food supplies, restriction of the activity of sick food handlers, and possibly isolation of sick individuals.

No specific therapy is available. Treatment is supportive, particularly hydration and electrolyte replacement.

***“Patients And Hospice Directors Must Make Tough Choices.”***

**9-5 LETTING GO OF THE ROPE—Aggressive Treatment, Hospice Care, and Open Access**

“Ironically, hospice patients are increasingly forced to give up effective palliative treatments (eg, total parenteral nutritional support) along with aggressive medical intervention.” Treatment options are often limited by economic constraints. Some hospices will accept only patients who are willing to forgo life-sustaining treatments, including chemotherapy and parenteral nutrition.

A few large hospices offer “open-access” care, which allows patients to add hospice care to their current medical treatment. This option is not available everywhere. Open access programs remain the exception. Only 3% of 4100 hospices have a daily census above 400, commonly considered the minimum requirement for open access.

Many patients fear that they will not receive enough medical services in hospice. Optimal end-of-life support often necessitates careful titration of opioids, antipsychotic, and anxiolytic drugs, which can sometimes require a doctor's presence. But few patients ever meet a physician after enrolling. There are no rules mandating the degree of physician involvement.

The only randomized trial to date examining standard cancer care both with and without hospice support showed no significant difference in survival, but did show significant improvements in quality of life when cancer care and hospice were combined.

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*Services provided by hospice will vary from community to community. Primary care clinicians should be aware of the services their local hospice provides. And be able and willing to supplement care if necessary. Individual physicians who refer to hospice should follow-up their patient in one way or another, and help coordinate care and ensure adequate palliation. They must know the local hospice personnel, and the extent of their ability to provide services.*

*Do not withdraw after referral.*

*Do not abandon your patient.*

*Local hospices merit financial support from primary care physicians and the community.*

*The paradigm is shifting. See the following articles.*

### ***“Vast Unmet Needs Among Aging And Dying Patients Have Driven The Growth Of Palliative Care In Hospitals”***

#### **9-6 HOSPITALS EMBRACE PALLIATIVE CARE**

Despite advances in medicine, there is a growing population of aging patients with complex health problems that are often poorly served by even the best of intensive care units. To help these patients, hospitals are turning to palliative care, which focuses on symptom management, communication, and other means to improve quality-of-life for patients and their families.

Vast unmet needs among aging and dying patients have driven the growth of palliative care in hospitals.

Cost pressures and limited capacity have forced hospitals to reconsider how they care for the most critically ill. Hospitals have adopted a model in which patients are treated and quickly discharged. Not all patients fit this model. Not every patient can be cured. Elderly patients who develop complications after admission may spend weeks or months in the intensive care unit. Daily costs are very high.

Palliative care is an alternative. It improves the quality-of-life in these patients. It brings appropriate care, as opposed to unnecessary, expensive, and futile care. Emerging evidence suggests that appropriate discussion of the goals of care among clinicians, patients, and families, as well as aggressive symptom management, improves the quality-of-care, reduces hospital costs, and shortens length of stay.

In a traditional intensive care setting, a patient may be seen by multiple specialists who communicate primarily through the patient's chart. There may be no physician coordinating care. Some symptoms or problems

facing the patient and family may be falling through the cracks. Communication between the health care team, the patient, and the family may be compromised. Palliative care, on the other hand, brings together an interdisciplinary team of physicians, nurses, and social workers who work closely together to assess the needs and wishes of the patients and family.

Unlike hospice, which provides only supportive care to terminally ill patients, palliative care is appropriate for any patient with complex medical needs. In addition to supportive care, palliative care can provide curative and life-prolonging treatments. “It is as appropriate for a 24-year old coming into the hospital with a new diagnosis of leukemia for whom the goal is cure, but who has an enormous symptom burden and family distress, as it is for a person with advanced dementia and repeated bouts of aspiration pneumonia.”

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*The paradigm is shifting. Patients are beginning to realize that the length of life is limited by nature. They may be now opting for comfort care in place of “I want everything done” care. Death is natural.*

*Wouldn't it be terrifying if we lived too long?*

*See the following account of how a local hospice has expanded its care.*

### ***Morphing Hospice into Hospice + Palliative Care***

#### **9-7 AN EXEMPLARY HOSPICE**

*Hospice & Palliative Care of Charlotte Region. (HPCCR—Charlotte NC)* is unique among hospice programs. It provides “open access” for the community. It will accept all patients who are appropriate for hospice care who may be turned away from other hospices due to the complex nature of their illness, their treatment plan, or the cost of their care.

It is not-for-profit. Not-for-profit hospices generally have as their mission to serve all patients even when they cannot access reimbursement for services. HPCCR does not discriminate based on race, gender, religion, ethnic origin, disability, age, sexual preference, or ability to pay.

The mission of HPCCR is to relieve suffering and improve quality of life and dignity of life through compassionate hospice care for those at the end of life, and palliative care for those with advanced illness.

HPCCR is approaching its 30<sup>th</sup> anniversary. It has grown exponentially. It now serves more than 900 patients per day. It serves eight counties in the south Piedmont region of North Carolina and one county in South Carolina. It employs over 300 seasoned experts in end-of-life care and has almost 400 volunteers.

Hospice staff includes a physician, nurse, social worker, certified nursing assistant, chaplain, grief counselor, and volunteers.

The palliative medicine program has a staff of 10 full-time physicians, 6 nurse practitioners, and maintains a research partnership with the Charlotte branch of the North Carolina University System. The Palliative Medicine Consultants program provides care for individuals with advanced illness who are in need of pain and symptom management. Consultations are provided in hospitals, skilled nursing facilities, assisted living communities, and



in the patient's home. Care can be offered in conjunction with curative treatment. The patient can have unlimited life expectancy.

HPCCR has a pediatric palliative care program *Kids Path* [registered trademark]—a service to support children who are ill themselves, or who are dealing with grief associated with death or illness in their families.

Read the full abstract.

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*Not all hospices are the same. Some of the larger ones are able to provide more care. I believe more hospices are morphing toward combining palliative care with terminal-life care.*

*We are proud of our full service local hospice. It has grown rapidly over the past decade into one of the largest and most advanced and comprehensive providers of palliative care medicine in the US. I believe it may serve as a model for other hospices wishing to expand their services.*

*Practical Pointers frequently abstracts trials of drugs and other therapies which benefit patients under certain circumstances. Often the number of patients needed to treat (NNT) to benefit one patient is as large as 50 or 100. A NNT of 10 is uncommon. The NNT by hospice/palliative care = 1. Every patient receives a benefit. Quite a record !*

### ***A Sensitive Marker Of Lifestyle Changes, And A Potential Target For Reducing Risk Of CHD***

#### **9-8 CHANGES IN TRIGLYCERIDE LEVELS AND RISK FOR CORONARY HEART DISEASE IN YOUNG MEN.**

This study assessed the association between baseline TG levels, and changes in TG over time, on risk of CHD in young men.

Entered over 13 500 apparently healthy men (mean age at baseline = 33; range 26 to 45). None were receiving lipid-lowering drugs. Obtained 2 measurements of fasting T—5 years apart. All TG levels were below 300 mg/dL at baseline. Estimated the effect of baseline TG levels (time 1), and changes (between time 1 and time 2) in TG levels on CHD risk.

Baseline characteristics by quintile of TG levels:

(Each quintile contained about 2800 persons. Mean follow-up ~ 10 years)

TG range (mg/dL)	30-66	67-90	91-119	120-163	164-299
Mean BMI	24	25	26	26	27
Physical activity (min/wk)	38	35	32	30	25
Habit of eating breakfast (%)	22	19	18	18	16
Incident cases of CHD	8	13	37	42	70

Another analysis divided subjects' TG levels by tertile (low; intermediate; high) in order to determine effect on incidence of CHD according to changes in TG levels obtained on 2 occasions 5 years apart. TG levels were classified as low (< 82 mg/dL; intermediate 82-130; and high > 130).

Among these men, changes in TG levels over 5 years were associated with alterations in BMI, physical

activity and eating breakfast:

BMI increased in men in the high-high TG group; BMI decreased in the high-low group

Physical activity increased in the high-low group

Frequency of breakfast eating remained stable in the low/low group; decreased in the low/high and high/high groups. (Ie, eating breakfast was a beneficial health habit.)

“These findings corroborate triglycerides as a sensitive marker of lifestyle changes.”

A presently low TG level would be associated with a 7-fold risk of CHD if a future TG level would place the patient in the low/high subgroup. A present TG level within the high level would be associated with an 8-fold risk of CHD if the TG level 5 years hence remained high; and a 5-fold risk of CHD even if the TG level 5 years hence were to become low (as compared with the stable low/low group).

Decreasing TG levels (high to low) in some individuals dramatically decreases CHD risk over a relatively short period.

. “Our study provides compelling evidence for the potential value of targeting triglyceride levels when trying to reduce CHD risk in young men. ”

Conclusion: Two TG measurements obtained 5 years apart may assist in assessing CHD risk in young men.

A decrease in initially elevated TG levels was associated with a decrease in CHD risk compared with stable high TG levels. However, this risk remained higher than those with persistently low TG levels.

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*We can no longer ignore triglycerides as a risk factor.*

**“Strongly Associated With CHD Risk”**

## **9-9 TRIGLYCERIDES AND CORONARY HEART DISEASE REVISITED**

*(This editorial comments and expands on the preceding article.)*

The results of the preceding study are striking. TGs were strongly associated with CHD risk. After 10 years of follow-up, those in the 5<sup>th</sup> quintile of TG levels had a hazard ratio for CHD of 4.0 compared with those in the lowest quintile. Even more strikingly, changes in TG levels over 5 years were associated with changes in risk.

Favorable life-styles—eating breakfast (“yes it helps”), losing weight, and increasing physical activity—were associated with reduced TG.

“The data complement the growing body of evidence that triglycerides have an independent effect on the incidence of CHD.” Elevated TG levels are not simply an epiphenomenon of insulin resistance in the metabolic syndrome.

Does treatment to reduce TG levels reduce CHD events? This is difficult to answer because all behavioral and pharmacological therapies for elevated TG also influence other lipids and lipoprotein fractions. However, clinical trials consistently show that patients with elevated TG levels receive the most benefit from lipid therapy regardless of the primary target of the specific therapy (LDL-c, HDL-c, or TG level). The Scandinavian Simvastatin Survival Study reported that persons with high LDL-c, accompanied by low HDL-c and high TG had

significant benefit from simvastatin therapy, whereas isolated high LDL-c did not, despite identical LDL-c reductions in both groups. Dual dyslipidemic therapy with a statin and niacin—the latter primarily affecting HDL-c and TG—provides particularly strong cardiovascular risk reduction.

For the public, the greatest concern is the obesity epidemic, which fuels TG levels and other metabolic syndrome components.

***“No One Should Fall Prey To The Temptation To Pit Science Against Religion. They Negotiate Different Domains”***

## **9-10 BEYOND THE TEACHABLE MOMENT: A Plea for Greater Understanding Between Science and the Public**

Despite many biomedical advances that are applauded by the public, there is increased tension in the broader relationship between science and the rest of society. The general public lacks an understanding of the nature of science and scientific evidence; there is a concomitant reluctance to demand an evidence base for medical treatments.

For science to truly serve society, biomedical scientists need to take advantage of all opportunities to engage more fully with the public.

Over one third of adults in the USA accept “alternative therapies” that are either not science-based or are completely untested. Science and its applications proceed at a slow pace. Frustrated, many individuals rush to alternative treatments. The hope for rapid relief trumps the need for evidence-based care.

Frequently people do not know the difference between evidence-based and non-evidenced-based treatments. “The plural of anecdote is not evidence.” Widespread publicity for the purported effectiveness of non-scientific treatments undermines the call for adherence to the science base. However, a call for an evidence base need not undermine patients’ choices, alternative strategies, or a holistic individualized approach to health care.

Science increasingly encroaches on issues related to core human values and strongly held beliefs. Science need not be at odds with religion. Science is limited to natural explanations of the natural world. Science should not be expected to be able to answer questions about the supernatural. No one should fall prey to the temptation to pit science against religion. They negotiate different domains.

The scientific community has much to learn from listening to diverse public perspectives. Ultimately, what public engagement means at its core is to listen as well as to educate patients.

“The most important principle . . . is to really listen to what advocates, patients, and other stakeholders have to say.” Listening well will be a challenge. The public has much to say, and biomedical scientists have much to learn.

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*Not all of our applications in primary care are firmly evidence-based. Medical advice has a way of changing. Guidelines and systematic reviews require revision every few years. Understandingly, at times the public is confused. The scientific approach requires self-correction.*

*I believe some advertisements in the lay press take advantage of the general public's lack of understanding. Note the outrageous claims of rapid weight loss by some charlatans who quote anecdotal testimonials by Lois M, or Dick J. They are here today, and gone tomorrow, displaced by even more outrageous claims. The October 23 issue of The Charlotte Observer quotes the November/December issue of Body + Soul magazine which presents "Popular Natural Remedies for Cold and Flu" including echinacea, elderberry, olive-leaf extract, astragalus, medicinal mushrooms, and oscillococcinum.*

*If the patient uses an "alternative therapy" and believes it helps him, I would not knock it as long as I found it harmless, and as long as it did not interfere with the application of treatment known to be effective.*

*I would not deny patients the power of the placebo. But, primary care clinicians should take the opportunity to demonstrate that something may work better.*

*I believe the statement by the author regarding pitting science against religion and faith is important. Science can neither prove nor disprove the meta-physical. We should be wary about criticizing faith as not-evidence-based. During my years of making hospital rounds, I would occasionally arrive at a patient's bedside at the same time the hospital chaplain or the patient's pastor arrived. When a prayer was offered, I would willingly join in. This would give me a spiritual uplift, and at the same time a feeling of being more emotionally connected with the patient. During my hospitalizations as a patient, a clergyman friend would visit and offer a short prayer. This would comfort me.*

*I believe studies attempting to disprove or prove the power of intercessional prayer are bound to failure.*

# ABSTRACTS SEPTEMBER 2007

## *Metformin and Sulfonylureas Win the Day*

### 9-1 COMPARATIVE EFFECTIVENESS AND SAFETY OF ORAL MEDICATIONS FOR TYPE 2 DIABETES A Systematic Review

As newer oral agents are increasingly marketed for treatment of type-2 diabetes (**DM2**), clinicians and patients must decide whether they prefer these generally more costly medications (eg, thiazolidinediones; meglitinides) or the older agents (metformin; sulfonylureas).

Heretofore, no systematic review has summarized all available head-to-head comparisons with regard to the full range of intermediate endpoints (HbA1c, lipids, and body weight), and other clinically important outcomes such as adverse effects and macro-vascular risks. (Several studies of treatment of DM2 have suggested that improved glycemic control reduces micro-vascular events. In contrast, the effects of treatment of macro-vascular events are more controversial.)

The Agency for Health Research and Quality commissioned this systemic review of English language literature to summarize the comparative benefits and harms of oral agents (second generation sulfonylureas; metformin; thiazolidinediones; meglitinides; and glucosidase inhibitors) for treatment of DM2 in adults.

Conclusion: Compared with the newer, more expensive agents, older agents (metformin and second-generation sulfonylureas) have similar or superior effects on glycemic control, lipids, and other intermediate endpoints. (Comparative effects on hard clinical endpoints are not yet available.)

## STUDY

1. This study summarized the benefits and harms of oral agents used in treatment of DM2:

2<sup>nd</sup> generation sulfonylureas (All 3 are generic)

- a. glyburide (formerly *Micronase*; *Diabeta*)
- b. glipizide (formerly *Glucotrol*)
- c. glimepiride (*Amaryl*)

Metformin (a biguanide; Generic; formerly *Glucophage*)

Thiazolidinediones (eg, rosiglitazone [*Avianda*] and pioglitazone [*Actos*])

Meglitinides (repaglinide [*Prandin*] and nateglinide [*Starlix*])

Alpha-glucosidase inhibitor (acarbose; *Precose*)

2. An extensive literature search selected 216 controlled trials and cohort studies, and 2 systematic reviews that addressed benefits and harms of oral drugs available in the USA for treatment of DM2 in adults.

## RESULTS

1. Evidence was inconclusive regarding major clinical endpoint (all cause mortality; cardiovascular mortality,

nonfatal MI and stroke, and micro-vascular outcomes).

2. This review therefore was limited to intermediate endpoints (eg, HbA1c; bodyweight; BP; lipids, and major adverse effects including hypoglycemia.

3. HbA1c:

When used as monotherapy, thiazolidinediones, sulfonylureas, repaglinide and metformin were associated with about a 1% reduction. Various combinations of metformin + sulfonylurea; metformin + thiazolidinediones; sulfonylurea + thiazolidinediones have additive effects—another 1% reduction compared with monotherapy. Nateglinide and alpha-glucosidase inhibitor produced weaker reductions.

4. Body weight:

Metformin long-term produced no weight gain as compared with placebo and other drugs.

Acarbose produced no weight gain compared with placebo.

5. Blood pressure:

Effects were minimal.

6. Lipids:

LDL-cholesterol: metformin decreased levels by about 10 mg/dL; thiazolidinediones increased levels; others had little effect.

HDL-cholesterol: thiazolidinediones increased levels slightly.

Triglycerides: compared with sulfonylureas rosiglitazone increased levels by about 10 mg/dL; other drugs decreased triglycerides by 10 to 30 mg/dL

7. Other adverse effects:

Hypoglycemia: major and minor hypoglycemic episodes were more common with sulfonylureas (especially glyburide).

Gastrointestinal: metformin and acarbose were associated with more g.i. adverse effects.

Lactic acidosis: rates were similar between metformin and other drugs.

Edema: thiazolidinediones were associated with edema.

Congestive heart failure: thiazolidinediones were associated with increased risk of heart failure.

Absolute risks were small—1% to 3%.

Elevated aminotransferase levels; generally low < 1% for metformin; sulfonylurea; and thiazolidinediones.

Allergic reactions: no serious allergic reactions were reported.

## DISCUSSION

1. Ideally, oral diabetes agents should improve microvascular and macrovascular outcomes and mortality.

“We found no definitive comparative evidence on these outcomes.”

2. Therefore, the study reported effects on intermediate outcomes and adverse effects.

3. “By these criteria, we found that metformin was similar to, or better than, other currently available oral agents.

Second-generation sulfonylureas also fared well against other agents apart from the increased risk of hypoglycemia.”

4. Compared with the newer agents, metformin and 2<sup>nd</sup> generation sulfonylureas share three additional advantages: 1) lower cost; 2) longer use in practice; and 3) more intensive scrutiny in long-term trials with relevant endpoints.
5. These findings support the current American Diabetes Foundation recommendations that favor metformin as initial oral pharmacotherapy for DM2.
6. Optimal glycemic control often requires multidrug therapy. A second agent is additive in terms of improved glycemic control. It also increases risk for adverse events “unless both agents are used at lower doses”.<sup>1</sup> Although sulfonylureas are not clearly superior to newer agents, they remain a reasonable alternative for second line therapy, especially if cost is an issue.<sup>2</sup>
7. Because of concerns about lactic acidosis, metformin is contraindicated in patients with impaired renal function and congestive heart failure. However, this review did not find any evidence of an elevated risk of lactic acidosis in patients taking metformin as compared with other oral agents. “We suspect that apparent cases of ‘metformin-induced lactic acidosis’ may have been over-reported”.
8. Each oral diabetes agent is associated with adverse effects that counterbalance its benefits. Overall metformin seemed to have the best benefit / harm ratio. (*And a high benefit /cost ratio. RTJ*)
9. Larger long-term studies on major clinical outcomes (MI, chronic kidney disease, cardiovascular mortality) are needed to determine definitively the comparative effects on oral agents.

## CONCLUSION

Compared with newer, more expensive agents, metformin and 2<sup>nd</sup> generation sulfonylureas have similar or superior effects on glycemic control and other cardiovascular risk factors (BP, lipids, and body weight).

Annals Int Med September 18, 2007; 147: 386-99 Review article, first author Shari Bolen, Johns Hopkins University, Baltimore MD.

This review was supported by The Agency for Healthcare Research and Quality, US Department of Health and Human Services, and the Centers for Education and Research on Therapeutics.

**1** I believe this is a good general principle. For treatment of any condition, when adding a second drug to a first drug, it is prudent to lower doses of both drugs to begin with. This will reduce likelihood of adverse effects. Doses may then be increased gradually.

**2** Some pharmacies offer a month’s supply of generic drugs for \$4. (Go to Google *\$4 prescriptions*). All the 2<sup>nd</sup> generation sulfonylureas and metformin are included in their list. Interestingly, the dose prescribed makes no difference in price—1000 mg of metformin #60 costs \$4, just as 500 mg #60 For many patients cost of drugs determines whether or not they will adhere with their prescribed treatment.

An editorial in this issue of Annals (pp 428-30) by Leonard M Pogach, VA Affairs, New Jersey Health Care System, East Orange, comments and expands

Because this review evaluated the entire body of evidence, the findings should shift readers away from relying too heavily on single studies. This applies especially to industry-sponsored studies that are often designed to increase the likelihood of a favorable result by the choice of a comparator group, dose, time course, and specified analysis (eg, analyzing only persons who complete a trial instead of all participants).

The major limitation of the review is that it excluded persons who cannot comply with a study protocol, or who have significant co-morbid conditions. Thus, generalizability is limited. Clinicians will have to use both the evidence and their clinical judgment to apply findings of the review. The patient must be a partner in the decision-making process which should weigh other factors such as costs and personal preferences.

We are obliged to provide patients with a careful assessment of the known risks and benefits of medications as well as the benefits of lowering HbA1c levels

The desired HbA1c level must be individualized. Current guidelines recommend that it not be lower than 7.0 % in persons over age 65, those that have co-morbid conditions, and those who have higher risk for adverse effects.

Physicians and patients should also be cautioned about intensifying oral medications on the basis of the last HbA1c result, especially if it is marginally above the patient's target level. A margin of measurement error around a single HbA1c value of 7% from a commercial laboratory can range from 6.5% to 7.5%. Small changes may be due to random variation.

If control is poor—substantially or consistently above target HbA1c levels—it is time to reevaluate medication adherence and lifestyle factors, and screen for depression. Absent these concerns, the current dose should be increased, or a second drug added.

Because DM2 is a progressive disease caused by beta-cell failure, many patients will eventually need insulin. Patients should be engaged early in dialogues about starting insulin to try to explain the relative benefits, risks, and costs.

Patients with DM2 should know that intensifying lipid and BP control often has a greater impact on length and quality of life than intensifying glycemetic control.

*Glucose control (determined by HbA1c) is not the most important factor determining outcomes in patients with DM2. See the following abstract.*

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***“The Apparent Benefits Of Surrogate Outcomes Are A Mirage”***

**9-2 PATIENT-IMPORTANT OUTCOMES IN DIABETES—Time For Consensus**

It has been 50 years since the first oral agent for type-2 diabetes (**DM2**) was introduced. We still remain uncertain if any antihyperglycemic drug can favorably affect key patient-important outcomes, including morbidity, mortality, and quality-of-life.

Diabetes trials have focused on the effects of interventions on glucose control (HbA1c levels) rather than on patient-important outcomes. Measurement of HbA1c purportedly captures the effect of therapy on diabetes complications—the lower the HbA1c, the lower the risk of complications. The Diabetes Control and Complications Trial offered the best evidence to support this putative link. In patients with type 1 diabetes,



DCCT established that near-physiological replacement of insulin lowered HbA1c concentrations and reduced the risk of micro-vascular complications (retinopathy, nephropathy, and neuropathy). And with less certainty, reduced risk of macro-vascular complications. In this context, HbA1c may be a credible surrogate endpoint.

Recent evidence that rosiglitazone raises cardiovascular risk has further reduced the credibility of HbA1c as an adequate surrogate.

Unfortunately, HbA1c loses its validity as a surrogate marker when patients have a constellation of metabolic abnormalities, when the most important common complications are macro-vascular. This situation characterizes DM2.

The history of medical therapeutics is littered with instances in which reliance on surrogate outcomes has provided misleading results. Despite these lessons, trialists continue to rely on surrogate outcomes to substitute for patient-important outcomes. The apparent benefits of surrogate outcomes are a mirage.

The direct measurement of patient-important outcomes in diabetes trials remains uncommon. If informed asymptomatic patients ask whether they will be better off if they follow a regimen which reduces HbA1c, the lack of high-quality evidence leaves us unable to provide a satisfactory response.

The medical community should insist that we invest the resources needed to do trials that ascertain the effect of interventions on patient-important outcomes.

Lancet September 29, 2007; 370: 1104-06 Comment, first author Victor M Montori, Mayo Clinic /college of Medicine, Rochester Minn.

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***Guiding Individual Patients in Their Pursuit of Dose Minimization***

**9-3 CAN DRUG REGIMENS BE ADAPTED TO PATIENTS, OR VICE VERSA?**

Drug non-adherence can lead to increased morbidity and mortality, reduced quality of life, and wasted health care resources. Systematic reviews reported that some types of intervention can improve drug adherence. The reported effects sizes were highly variable.

This commentary offers a new piece of the puzzle. It starts with a recognition that drug non-adherence is often intentional. Many people change their regimens because they have concerns about their drugs. Besides stopping medications altogether, patients may start to take drugs symptomatically or strategically, adjust dose to reduce unwanted consequences, or make regimens more socially acceptable. Such modifications show a desire to keep drug use to a minimum. This is sometimes evident from supplementation or replacement of a drug treatment with non-drug measures, or non-conventional remedies.

These editorialists propose that prescribers not only need good communication skills for pursuing concordance, but could also benefit from evidence about the potential advantages and risks of guiding individual patients in their pursuit of dose minimization instead of always attempting to enforce compliance.

Minimum effective doses can vary with individual differences in body weight, organ functions, and pharmacogenetic properties. Dose recommendations in package inserts and textbooks have often been derived from pivotal clinical trials that were not designed to establish minimum effective doses in individuals. Lower daily doses and taking the prescribed drug less often than every day may be just as effective, and associated with fewer adverse effects.

There are important cautions about the approach to pursue minimization. It must be possible to evaluate whether dose minimization is applicable, and to evaluate whether it leads to under-dosing. This is feasible when the drug is taken for symptomatic relief, and when an intermediate outcome can be easily and reliably monitored (as with BP). When determination of intermediate outcomes are not possible, support for minimization becomes inappropriate. It is important to determine whether the risk of temporary dose-reduction will entail health hazards.

An individualized approach may require extra time, doctor visits and laboratory measurements. In contrast, it may lessen non-compliance and thus improve outcomes.

Another potentially important benefit of minimization is that patients may feel that they are being taken more seriously, and may find that the standard dose is required after an attempt to individualize dose reduction fails.

Lancet September 8, 2007; 370: 813-14 “Comment”, first author Peter A G M DeSmet, University Medical Center, Nijmegen, Netherlands.

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***“The Most Common Cause Of Non-Bacterial Gastroenteritis”***

**9-4 NOROVIRUSES—CHALLENGES TO CONTROL**

Acute infectious gastroenteritis is second in frequency to acute respiratory illness. Laboratory studies over the past 3 decades have identified viruses as causative agents. Among the most prominent are a novel group of RNA viruses originally referred to as Norwalk-like agents—named after Norwalk Ohio, where an outbreak of illness was caused by the prototype agent—now called noroviruses.

There is no satisfactory animal model for norovirus disease. This hampers progress of vaccine development. Human noroviruses have not been cultured *in vitro*. Transfection<sup>1</sup> with viral RNA into human embryonic kidney cells has been reported. The characteristics and pathogenesis of noroviruses have been elucidated largely through studies of disease in humans and molecular analysis of virus from human stool samples. Several techniques can detect virus in the stools.

With increased ability to detect the virus, noroviruses are now recognized as the most common cause of non-bacterial gastroenteritis. In the US between 1997-2000, of 233 gastroenteritis outbreaks, 93% were due to the norovirus. Although the CDC does not conduct surveillance, it estimates that at least 23 million cases occur annually in the U.S. Frequency, seasonality, and geographic location of outbreaks vary substantially from year to year.

The illness usually entails both vomiting and diarrhea (4 to 8 non-bloody stools daily), often accompanied by nausea, abdominal cramps, and systemic symptoms. Fever (usually low grade) is present in about half the cases. Manifestations usually last one to three days. They are usually mild and self-limiting. But, at the height of the illness, symptoms may be incapacitating.

The incubation period is one to 2 days, although shorter periods have been described.

The infection can occur sporadically in individuals, in small family groups, and among people in closed settings (cruise ships, nursing homes, army installations, hospitals). The median size of an outbreak is 25 people. Some outbreaks have been reported to affect hundreds of thousands.

Infection may be spread person-to-person, or be waterborne or foodborne. Foodborne transmission has been particularly prominent (up to 50% of outbreaks). A wide variety of foods have been implicated. Shellfish can efficiently concentrate the virus from contaminated water. Secondary transmission occurs in many outbreaks, appearing to occur mainly through the fecal-oral route. Respiratory spread has been suspected, but not proved.

Virus shedding can occur for a few days before symptoms, and continue after symptoms cease. This complicates management of outbreaks.

Susceptibility to the infection is widespread. Immunity is poorly understood. Resistance develops to the same strain of the virus, but not to other strains. (The virus is genetically diverse.) Immunity to the infecting strain lasts up to several years.

Noroviruses are extremely infectious. As few as 10 particles may be needed to cause infection. They are highly resistant to inactivation by freezing, heating to 60<sup>0</sup> C, exposure to chlorine in concentrations of 1.0 mg/liter, pH levels of 2.7, and treatment with ether, ethanol<sup>2</sup>, and detergent-based cleaners. Steaming of shellfish does not entirely eliminate the risk of transmission. Solutions of hypochlorite at 500 ppm are effective decontamination.

The primary control measures are environmental decontamination, prevention of contamination of water and food supplies, restriction of the activity of sick food handlers, and possibly isolation of sick individuals.

No specific therapy is available. Treatment is supportive, particularly hydration and electrolyte replacement.

NEJM September 13, 2007; 357: 1072-73 “Perspective”, commentary by Raphael Dolin, Harvard Medical School, Boston, Mass.

**1** It is my first encounter with this word. I thought at first that it was a misprint. It means infection of a cell with purified viral nucleic acid resulting in replication of the virus in the cell. Or, more generally, incorporation of exogenous nucleic acid into a cell.

**2** This is a little discouraging for us who rely on regular hand decontamination with alcohol-containing hand washes. I would like to know more.

A communication from the CDC (MMWR 2007;56: 842-46) abstracted in the JAMA October 10 2007 updates norovirus activity in the United States:

More outbreaks are being reported even though no national surveillance system exists. New strains are appearing. Deaths are being reported. A large proportion of cases occurred among residents of long-term-care facilities.

Transmission occurs through contact with contaminated environmental surfaces as well as via foodborne and person-to-person contact. Shared toilet facilities, close living quarters, and immobile or incontinent residents predispose to transmission.

Recommended measures for prevention and control:

- Practice good hand hygiene. Wash with soap and water Use alcohol-based gel with at least 62% ethanol content
- Disinfect contaminated surfaces (eg with chlorine bleach)
- Do not return to work or school until 24 to 72 hours after symptoms resolve
- Avoid sharing staff members between units
- Group symptomatic patients and provide separate toilet facilities. Close affected units to new admissions
- Instruct visitors on appropriate hand hygiene

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### **“Patients And Hospice Directors Must Make Tough Choices.”**

#### **9-5 LETTING GO OF THE ROPE—Aggressive Treatment, Hospice Care, and Open Access**

“Ironically, hospice patients are increasingly forced to give up effective palliative treatments (eg, total parenteral nutritional support) along with aggressive medical intervention.” Treatment options are often limited by economic constraints. Some hospices will accept only patients who are willing to forgo life-sustaining treatments, including chemotherapy and parenteral nutrition.

Some hospices are small, caring for relatively few patients with a limited staff, at times working part time. A small program cannot negotiate pricing or spread the costs of expensive medications across many patients.

A few large hospices offer “open-access” care, which allows patients to add hospice care to their current medical treatment. This option is not available everywhere. Open access programs remain the exception. Only 3% of the countries 4100 hospices have a daily census above 400, commonly considered the minimum requirement for open access.

Medicare reimburses hospices on a per diem basis, paying fixed fees regardless of services provided. Fees have not kept up with the cost of cutting-edge palliative treatments. Many patients who meet criteria for hospice care still opt for continued chemotherapy, radiation, antiemetics, or blood transfusions. These can cost more than \$10 000 per month. Open access may be prohibitively expensive. “Patients and hospice directors must make

tough choices.” “We’ve got to begin grappling with tough choices if we’re going to stay in business for \$150 a day.”

Most patients wait until the last few weeks of life to enroll. One contributing factor is late referrals by oncologists, who routinely overestimate patients’ lifespans. “Many patients are referred only when no other option remains.”

Many patients fear that they will not receive enough medical services in hospice. Optimal end-of-life support often necessitates careful titration of opioids, antipsychotic, and anxiolytic drugs, which can sometimes require a doctor’s presence. But few patients ever meet a physician after enrolling. There are no rules mandating the degree of physician involvement.

Each hospice program decides what services to offer, and family members often must fill in the gaps.

Some families may become angry if there is a forced choice between parenteral nutrition and hospice care. They believe the patient might have suffered less in an open-access hospice program “Open access gives people the choice to let go of active treatment with one hand and grab on to the hospice rope until they feel comfortable letting the other hand go.”

The only randomized trial to date examining standard cancer care both with and without hospice support showed no significant difference in survival, but did show significant improvements in quality of life when cancer care and hospice were combined.

NEJM July 26, 2007; 357: 324-27 “Perspective”, commentary, first author Alexi A Wright, Dana-Farber Cancer Institute, Boston Mass.

*The paradigm is shifting. See the following articles.*

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***“Vast Unmet Needs Among Aging And Dying Patients Have Driven The Growth Of Palliative Care In Hospitals”***

## **9-6 HOSPITALS EMBRACE PALLIATIVE CARE**

Despite advances in medicine, there is a growing population of aging patients with complex health problems that are often poorly served by even the best of intensive care units. To help these patients, hospitals are turning to palliative care, which focuses on symptom management, communication, and other means to improve quality-of-life for patients and their families.

Palliative care may be delivered in concert with curative or life-prolonging medical care. It is not prognosis dependent. “These features distinguish it from hospice care, which offers symptom management for patients who are facing a terminal illness and no longer wish to undergo life-prolonging treatments.”

The number of hospitals with palliative care programs is expanding rapidly. The field of palliative and hospice care became formally recognized as a subspecialty by the American Board of Medical Specialties in 2006. Also in 2006, the Accreditation Council for Graduate Medical Education began accrediting hospice and

palliative medicine fellowship programs. In 2008, physicians will be able to become board certified in hospice and palliative care.

Vast unmet needs among aging and dying patients have driven the growth of palliative care in hospitals. Not every patient can be cured.

Technology has blurred the line between illness and the end of life. How and when should life-prolonging technology be used? When should its use end? Who should make the decision?

The Institute of Medicine has outlined concerns about deficiencies in the way seriously ill and dying patients are treated:

- Needless suffering at the end of life when patients may not receive appropriate supportive care, or when they receive unnecessary or ineffective treatments.
- Legal, organizational, and economic factors that impede the delivery of the best care for these individuals.
- Inadequate education of health care professionals about end-of-life care.
- Lack of research to support evidence-based end-of-life care.

Cost pressures and limited capacity have forced hospitals to reconsider how they care for the most critically ill. Hospitals have adopted a model in which patients are treated and quickly discharged, Not all patients fit this model. Elderly patients who develop complications after admission may spend weeks or months in the intensive care unit. Daily costs are very high.

Palliative care is an alternative. It improves the quality-of-life in these patients. It brings appropriate care, as opposed to unnecessary, expensive, and futile care. Emerging evidence suggests that appropriate discussion of the goals of care among clinicians, patients, and families, as well as aggressive symptom management, improves the quality-of-care, reduces hospital costs, and shortens length of stay.

In a traditional intensive care setting, a patient may be seen by multiple specialists who communicate primarily through the patient's chart. There may be no physician coordinating care. Some symptoms or problems facing the patient and family may be falling through the cracks. Communication between the health care team, the patient, and the family may be compromised. Palliative care, on the other hand, brings together an interdisciplinary team of physicians, nurses, and social workers who work closely together to assess the needs and wishes of the patients and family. And to establish and carry out a treatment plan accordingly. The team places special emphasis on assessing and managing pain, anxiety, depression, insomnia, constipation, and shortness of breath. To ensure good communication, the team also gathers information from all the treating physicians and translates it into language that the patient, family and the primary-care physician understand.

For patients who wish to be treated at home, the team brings planning and carrying out an effective, safe, and sustainable plan. This may greatly reduce readmissions to the hospital.

Unlike hospice, which provides only supportive care to terminally ill patients, palliative care is appropriate for any patient with complex medical needs. In addition to supportive care, palliative care can provide curative and life-prolonging treatments. "It is as appropriate for a 24-year old coming into the hospital with a new diagnosis of

leukemia for whom the goal is cure, but who has an enormous symptom burden and family distress, as it is for a person with advanced dementia and repeated bouts of aspiration pneumonia.”

Recent growth of home hospice care has allowed more individuals to chose to die at home. Most US residents report they would prefer to die at home. This goal is far from being achieved.

The American Academy of Hospice and Palliative Medicine, begun in 1988, has grown to include more than 2600 members. The number of fellowships in palliative and hospice care is growing. The Academy is working to gain funding sources for fellowship training. Another key priority is convincing the Centers for Medicare and Medicaid Services to recognize palliative care as a subspecialty. Data have begun to show quality improvements and cost savings associated with palliative care. Continued growth of palliative care programs will lead to high quality care for the most vulnerable patients. “It’s a win-win.”

JAMA September 19, 2007; 298: 1263-65 “Medical News and Perspectives”, commentary by Bridget M Kuehn, JAMA staff.

*See the following account of how a local hospice has expanded its care.*

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### ***Morphing Hospice into Hospice + Palliative Care***

#### **9-7 AN EXEMPLARY HOSPICE**

*Hospice & Palliative Care of Charlotte Region. (HPCCR—Charlotte NC)* is unique among hospice programs. It provides “open access” for the community. It will accept all patients who are appropriate for hospice care who may be turned away from other hospices due to the complex nature of their illness, their treatment plan, or the cost of their care.

It is not-for-profit. Not-for-profit hospices generally have as their mission serving all patients, even when they cannot access reimbursement for services. HPCCR does not discriminate based on race, gender, religion, ethnic origin, disability, age, sexual preference, or ability to pay.

The mission of HPCCR is to relieve suffering and improve quality of life and dignity of life through compassionate hospice care for those at the end of life, and palliative care for those with advanced illness.

HPCCR is approaching its 30<sup>th</sup> anniversary. It has grown exponentially. It now serves more than 900 patients per day.

Outreach and staff:

HPCCR serves eight counties in the south Piedmont region of North Carolina and one county in South Carolina. It employs over 300 experts in end-of-life care and has almost 400 volunteers.

It served over 1800 hospice patients and over 1900 palliative care patients in 2006. The palliative care service for non-hospice patients living with serious disease has expanded.

HPCCR has a specialized pediatric team, an extensive bereavement program, and a specialized long-term care team.

The *Kids Path* [Registered trademark] program offers specialized health care and support services to children who are coping with serious illness, and to their families. Care may be focused on cure or comfort.

A new free-standing Hospice House provides inpatient care. It is a haven for those who cannot be cared for at home or who may need interim care in a home-like setting.

The palliative medicine program has a staff of 10 full-time physicians, and 6 nurse practitioners. It maintains a research partnership with the Charlotte branch of the North Carolina University System.

Hospice staff includes a physician, nurse, social worker, nursing assistant, chaplain, grief counselor, and volunteers.

#### Hospice care:

For patients with a life expectancy of six months or less, if the illness takes its expected course.

Goals focus on comfort measures rather than cure. But may include aggressive therapies such as select chemotherapy and radiation.

Applies an interdisciplinary team approach for physical, emotional, and spiritual support, including grief and symptom management and discussions about end of life.

Compassionate and holistic comfort care is provided to enhance the quality and dignity of life. This may increase the patients' desire to continue living and may make them feel like less of a burden on family members. Support and training is provided to family caregivers as well.

Patients are seen in hospitals, long-term care facilities, assisted living communities, and in their own homes.

Terminally ill Medicare beneficiaries desiring hospice care may elect the hospice Medicare benefit. The benefit is not intended to cover experimental or curative therapies. It provides expanded coverage for treatment of symptoms arising from terminal illness including: heart disease, pulmonary disease, kidney disease, stroke, coma, liver disease, dementia (including Alzheimer's), HIV/AIDS, and failure to thrive, as well as cancer.

Reimbursement is by per diem from Medicare, Medicaid, (and private insurance if available). There are two benefit periods of 90 days each, followed by an unlimited number of 60-day benefit periods. At the end of each period, the patient is reevaluated to certify that the condition still meets the requirements of the benefit. Services are provided regardless of ability to pay.

North Carolina also has a hospice Medicaid benefit.

Medicare/Medicaid payment is made to the hospice provider on the basis of one of 4 daily rates based on the level of care provided. Covered services must be related to managing symptoms of the terminal illness.

If the patient elects the Medicare/Medicaid benefit, additional services are included: durable medical equipment, medical supplies, prescription medications, consulting physician services, palliative IV therapy, and ambulance transportation as reimbursable under regular Medicare.



Palliative care:

Palliative medicine is a medical specialty that focuses on alleviating pain and other symptoms of illness, especially complicated conditions, symptoms of which are difficult to relieve, long term, and incurable. It also addresses psychological, social, and spiritual concerns of patients and their families.

Referrals are made by the patient’s private physician who continues all other appropriate disease-directed medical treatment. Life expectancy may not be defined.

Care can be offered simultaneously with all other appropriate medical care. Consultations are provided in hospitals, skilled nursing facilities, assisted living communities, and in the patient’s home.

Goals focus on palliation of symptoms. But, may also include cure or active management of the disease.

Patients who benefit from palliative care include those with uncontrolled symptoms: pain, dyspnea, nausea/vomiting, delirium, insomnia, anxiety, agitation.

Medications, supplies, and equipment may be covered by patient’s insurance.

Reimbursement for physician/nurse practitioner consultations may come from Medicare, Medicaid, and private insurance. Services are provided regardless of ability to pay.

Care of children:

HPCCR is associated with *Kids Path*. [Registered trademark]

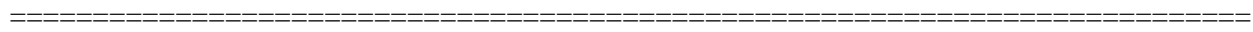
*Kids Path*, founded in Greensboro, NC offers services in three states, in 7 cities in NC, and in Charleston SC.. It is a unique program for children and teens and their families facing the challenges of coping with a serious progressive illness. Children who are ill themselves, or who are dealing with grief associated with death or illness in their families, need special care and support. Children and teens cope with illness and loss differently than adults. *Kids Path* strives to meet their unique needs.

*Kids Path* interdisciplinary team offers nursing, home care, health counseling, and spiritual and grief support to children and families. It provides palliative medicine consultation, home health care, hospice care, grief counseling, and a grief camp for children.

Volunteers:

Volunteers provide patient companionship and relief to care givers, transportation, assistance at fund raising, and office assistance. More than 400 volunteers provided over 22 000 hours of compassionate care in 2006. Teen-agers are welcome as volunteers and are able to experience direct involvement with patient care.

Personal communication from Janet T. Fortner, MSW, President and CEO HPCCR.



## *A Sensitive Marker Of Lifestyle Changes, And A Potential Target For Reducing Risk Of CHD*

### **9-8 CHANGES IN TRIGLYCERIDE LEVELS AND RISK FOR CORONARY HEART DISEASE IN YOUNG MEN.**

Most published papers suggest a moderate association between fasting triglyceride (TG) levels and coronary heart disease (CHD). “A considerable increase in the proportion of hyper-triglyceridemia patients accompanies the obesity epidemic.”

Of the lipid fractions, the TG-rich very-low-density lipoprotein particle is probably the most sensitive to lifestyle modification. Weight loss and aerobic exercise lower levels.

When assessing the risk associated with TG levels, measurement at a single time point (typically at enrollment) may not be a reliable indicator of a person’s TG levels during long-term follow-up.

Whether changes in TG levels over time affect cardiovascular risk is unknown, particularly in young adults.

This study assessed the association between baseline TG levels, and changes in TG over time, on risk of CHD in young men.

Conclusion: Two measurements of TG obtained 5 years apart may assist in assessing CHD risk in young men.

#### **STUDY**

1. Entered over 13 500 apparently healthy men (mean age at baseline = 33; range 26 to 45). None were receiving lipid-lowering drugs.
2. Obtained 2 measurements of fasting TG 5 years apart. All TG levels were below 300 mg/dL at baseline.
3. Personnel over age 35 received a treadmill exercise test. Those positive received coronary angiography.
4. Followed all for incident cases of angiographically proven CHD.
5. Estimated the effect of baseline TG levels (time 1), and changes (between time 1 and time 2) in TG levels on CHD risk.

#### **RESULTS**

1. Baseline characteristics by quintile of TG levels:

(Each quintile contained about 2800 persons. Mean follow-up ~ 10 years)

TG range (mg/dL)	30-66	67-90	91-119	120-163	164-299
Mean BMI	24	25	26	26	27
Physical activity (min/wk)	38	35	32	30	25
Habit of eating breakfast (%)	22	19	18	18	16

*(Note the association of TG levels with increasing weight, reduced exercise, and skipping breakfast. The authors did not comment on the reason for the association with breakfast. I presume that excessive food intake later in the day as a result of earlier fasting is a reason. RTJ )*

2. Multivariate hazard ratios of CHD by baseline quintile of TG:

(TG 30-66 = reference)	1.00	1.04	2.92	3.18	4.05
3. Incident cases of CHD	8	13	37	42	70

*(Almost all determined by angiography.)*

4. Another analysis divided subjects' TG levels by tertile (low; intermediate; high) in order to determine effect on incidence of CHD according to changes in TG levels obtained on 2 occasions 5 years apart. TG levels were classified as low (< 82 mg/dL; intermediate 82-130; and high > 130).

A. Low at time 1; low at time 2 (low/low group; TG remained stable at a low level over time)

Population at risk	2846
Events	4
Incidence / 10 000	14
CHD Hazard ratio	1.00 (reference)

B. Low at time 1; high at time 2 (low/high group; TG increased over time )

Population at risk	388
Events	6
Incidence / 10 000	155
Hazard ratio	6.8

C. High at time 1; low at time 2 (high/low group; TG decreased over time)

Population at risk	402
Events	5
Incidence / 10 000	124
Hazard ratio	4.90

D. High at time 1; high at time 2 (high/high group; TG remained high over time)

Population at risk	2840
Events	56
Incidence / 10 000	197
Hazard ratio	8.23

(Differences related to intermediate group were in between)

## DISCUSSION

1. Information on TG levels obtained at two times (5 years apart) were clinically relevant for assessing risk of CHD.
2. Among these men, changes in TG levels over 5 years were associated with alterations in BMI, physical activity and eating breakfast:
  - BMI increased in men in the high-high TG group; BMI decreased in the high-low group
  - Physical activity increased in the high-low group
  - Frequency of breakfast eating remained stable in the low/low group; decreased in the

low/high and high/high groups. (Ie, eating breakfast was a beneficial health habit.)

“These findings corroborate triglycerides as a sensitive marker of lifestyle changes.”

3. However, a substantial proportion of the CHD risk remained attributable to changes in TG levels during the subsequent 5 years of follow-up, independent of the associated alterations in BMI and lifestyle habits. TG might be a valuable biomarker of lifestyle. But, TG levels also exert life-style-independent effects on atherosclerosis.
4. A presently low TG level would be associated with a 7-fold risk of CHD if a future TG level would place the patient in the low/high subgroup. A present TG level within the high level would be associated with a 8-fold risk of CHD if the TG level 5 years hence remained high; and a 5-fold risk of CHD even if the TG level 5 years hence were to become low (as compared with the stable low/low group).
5. Atherosclerosis begins in childhood and progresses gradually throughout adulthood. Increased TG levels are directly associated with atherogenic chylomicrons and very-low-density lipoprotein remnants.
6. Decreasing TG levels (high to low) in some individuals dramatically decrease CHD risk over a relatively short period. In the young age group, high TG levels may identify persons exhibiting accelerated atherosclerosis, resulting in clinically evident CHD in the mid-40s.
7. The National Health and Nutrition Examination Survey (USA) showed a similar increase in mean age-adjusted TG levels in the US population between 1988 and 2002. This was likely due to increasing prevalence of obesity.
8. “Our study provides compelling evidence for the potential value of targeting triglyceride levels when trying to reduce CHD risk in young men. ”

## CONCLUSION

Two TG measurements obtained 5 years apart may assist in assessing CHD risk in young men.

A decrease in initially elevated TG levels was associated with a decrease in CHD risk compared with stable high TG levels. However, this risk remained higher than those with persistently low TG levels.

Annals Int Med September 18, 2007; 147: 377-85 original investigation by the MELANY (Metabolic Lifestyle, and Nutrition Assembly in Young Adults) study. First author Amir Tirosh, Sheba Medical Center, Tel-Hashomer, Israel, and the Israel Defense Forces Medical Corps.

All career Israel Defense Force staff are evaluated every 5 years between age 25 and 35 and every 3 years thereafter until discharged.

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## ***“Strongly Associated With CHD Risk”***

### **9-9 TRIGLYCERIDES AND CORONARY HEART DISEASE REVISITED**

*(This editorial comments and expands on the preceding article.)*

“The specific association of triglycerides with incident CHD has arguably generated more disagreement than any other measure.” Contradictory results abound and positive studies typically show a modest effect size.

Two published meta-analyses (1996 and 2007) concur that TG is an independent risk factor for CHD, even after adjustment for HDL-cholesterol (which is strongly and inversely correlated with TG levels). The first meta-analysis reported an overall relative risk for CHD of 1.2 for men and 1.4 for women per 89 mg/dL of TG. The second showed a relative risk of 1.4 comparing the top TG tertile with the bottom.

The most consistent findings have been higher relative risk in women, in those with low LDL-cholesterol, in those with diabetes, and in young persons. The effect on younger persons is of particular interest because aging has complex effects on cardiovascular risk-factor associations..

The results of the preceding study are striking. TGs were strongly associated with CHD risk. After 10 years of follow-up, those in the 5<sup>th</sup> quintile of TG levels had a hazard ratio for CHD of 4.0 compared with those in the lowest quintile.

Even more strikingly, changes in TG levels over 5 years were associated with changes in risk.

Favorable life-styles—eating breakfast (“yes it helps”), losing weight, and increasing physical activity—were associated with reduced TG.

The authors comment that the changes in CHD risk associated with changes in TG levels seemed to reflect cumulative exposure over the entire study.

“The data complement the growing body of evidence that triglycerides have an independent effect on the incidence of CHD.” Elevated TG levels are not simply an epiphenomenon of insulin resistance in the metabolic syndrome.

The villain may be the atherogenic lipoprotein remnants that accompany TG elevations. Recently non-fasting TG levels have been reported to be strongly correlated with levels of remnant lipoprotein cholesterol, and non-fasting TG levels predicted incident CHD events better than fasting TG. A standard post-meal TG level may be the best way to measure the atherogenic potential of TGs. <sup>1</sup>

Does treatment to reduce TG levels reduce CHD events? This is difficult to answer because all behavioral and pharmacological therapies for elevated TG also influence other lipids and lipoprotein fractions. However, clinical trials consistently show that patients with elevated TG levels receive the most benefit from lipid therapy regardless of the primary target of the specific therapy (LDL-c, HDL-c, or TG level). The Scandinavian Simvastatin Survival Study reported that persons with high LDL-c, accompanied by low HDL-c and high TG had significant benefit from simvastatin therapy, whereas persons with isolated high LDL-c did not benefit, despite identical reductions of LDL-c in both groups. Dual dyslipidemic therapy with a statin and niacin—the latter primarily affecting HDL-c and TG—provides particularly strong cardiovascular risk reduction.

For the clinician, these data emphasize the importance of “rediscovering ” triglycerides as a risk factor.

Weight loss and exercise are a crucial part of treatment directed at high TG levels.

For the public, the greatest concern is the obesity epidemic, which fuels TG levels and other metabolic syndrome components.

Annals Int Med September 18, 2007; 147: 425-27 Editorial by Michael H Criqui, University of California, San Diego CA

1 “Fasting Compared with Non-fasting Triglycerides and Risk of Cardiovascular Events in Women” JAMA July 18, 2007; 298: 299-308 Practical Pointers July 2007 [7-6]

“Triglycerides and Risk of Coronary Heart Disease” JAMA July 18, 2007; 298: 336-38 Practical Pointers July 2007 [7-7]

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***“No One Should Fall Prey To The Temptation To Pit Science Against Religion. They Negotiate Different Domains”***

## **9-10 BEYOND THE TEACHABLE MOMENT: A Plea for Greater Understanding Between Science and the Public**

Despite many biomedical advances that are applauded by the public, there is increased tension in the broader relationship between science and the rest of society. The general public lacks an understanding of the nature of science and scientific evidence; there is a concomitant reluctance to demand an evidence base for medical treatments.

For science to truly serve society, biomedical scientists need to take advantage of all opportunities to engage more fully with the public.

### The Nature and Need for Evidence:

Over one third of adults in the USA accept “alternative therapies” that are either not science-based or are completely untested. Science and its applications proceed at a slow pace. Frustrated, many individuals rush to alternative treatments. The hope for rapid relief trumps the need for evidence-based care.

Frequently people do not know the difference between evidence-based and non-evidenced-based treatments. “The plural of anecdote is not evidence.” Widespread publicity for the purported effectiveness of non-scientific treatments undermines the call for adherence to the science base. However, a call for an evidence base need not undermine patients’ choices, alternative strategies, or a holistic individualized approach to health care.

Most individuals have little understanding of the nature of science. A majority of Americans believe in extrasensory perception, believe that astrology is somewhat scientific, and that humans did not evolve from earlier animal species. They are unable to explain how an experiment is conducted. Some U.S. parents resist providing their daughters with the first human cancer vaccine because they fear it will endorse premarital sex. Rumors remain about a link between the M-M-R vaccine and autism, although a link has not been established.

The public does not understand the nature of science (and the nature of scientific evidence) and why evidence is so critical. This is a significant source of the tension in the broader relationship between science and society.

#### Science and Human Values:

Science increasingly encroaches on issues related to core human values and strongly held beliefs. Science need not be at odds with religion. But at times it appears that an almost anti-scientific attitude is prevailing. About 50% of Americans believe that “we depend too much on science and not enough on faith”. And that “scientific research these days does not pay enough attention to the moral values of society”. Opinions differ about when life begins, and debates about use of embryonic stem cells continue.

Many individuals do understand the basic research concept; they just do not like it

#### Exploit the Teachable Moment:

Both researchers and practitioners have many opportunities to educate the public. Educational efforts need to go beyond the traditional approach of teaching patients about specific research findings or the organ system affected by the ailments. The Institute for Medicine emphasizes the need for improved communication about the nature of evidence and its development, and the active role of both patients and health care professionals in evidence development and dissemination. (Primary care clinicians have many opportunities to discuss science and scientific evidence with patients, families, and through participation in community groups.) The fundamental principles of public engagement are to recognize the legitimate perspectives of the public and to view interactions as opportunities for science-society dialogues in which both listen and learn. However, tension points may not be fully resolved. (Persons who object to embryonic stem cell research on religious grounds likely will not change their minds no matter what the quality of dialogue.) “Experience also demonstrates that there is much more common ground than biomedical specialists might expect.” The scientific community has much to learn from listening to diverse public perspectives. Ultimately, what public engagement means at its core is to listen as well as to educate patients. It is deceptively difficult to understand points of common ground and points of irreducible conflict.

#### Principles of Engagement:

One of the most important principles is to be clear about the nature of science. It is necessary to be transparent in discussing the criteria for something to be considered scientific, and the limitations of science. Science is limited to natural explanations of the natural world. Science should not be expected to be able to answer questions about the supernatural. No one should fall prey to the temptation to pit science against religion. They negotiate different domains.

Stick to the scientific evidence. Issues such as stem cells involve both factual and value components. Scientists are expected to leave their personal values and beliefs behind and focus on the facts. This is important

for the sake of ensuring credibility. It is difficult to do well. Scientists are also human and have personal values that are often strongly held.

“The most important principle . . . is to really listen to what advocates, patients, and other stakeholders have to say.” Listening well will be a challenge. The public has much to say, and biomedical scientists have much to learn.

Significant attitudinal shifts and some behavior changes are required. Traditional approaches for communication and engagement are not working well enough. The science-society relationship is in a fragile period. It is time to evolve current strategies for engaging and communicating with the public. This will enable biomedical researchers to serve society more fully at the same time science is advancing.

JAMA September 19, 2007; 298: 1326-28 “Commentary” by Alan I Leshner, American Association for the Advancement of Science, Washington DC.

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