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FOR

PRIMARY CARE MEDICINE

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PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA

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26th YEAR OF PUBLICATION

This document is divided into two parts

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

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

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

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

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

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* AUGUST 2011

"We Need A New Approach To Proxy Measures Of Health."

8-1 SURROGATES UNDER SCRUTINY

We live in a time when disease is measured *not* by symptoms, but by numbers determined by biomarkers. Transferring a healthy person's risk of disease into a chronic condition has become a key characteristic of modern medicine, creating vast new markers for "preventive" pills designed to reduce suffering and extend life.

Well funded campaigns urge the public to "know your numbers" and "treat to target".

But the grand assumption underlying this approach—that helping patients' numbers will automatically improve their health—is a delusion as dangerous as it is seductive.

Whether we help or harm depends on how we lower risk—and long term treatments often carry unintended consequences. Even when significant clinical benefits are proved, the often minimal risk reductions associated with long term treatment suggest that the current approach may be over-medicating for little gain at great cost.

We have been too eager to accept favorable changes in biomarkers as a proxy for patient benefit. The focus on "knowing your numbers" and "treat to target" has seemed to be in everyone's best interest.

Simple assumptions about surrogate outcomes are often incorrect. We need to better inform patients about potential harms. If a drug is approved only on the evidence of its impact on a biomarker, there should be clear warnings that it has unproven effects on patient health.

Recently, the Institute of Medicine issued *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease.*[1] It is sobering. It details the often misplaced confidence when relying on surrogate endpoints to assess treatment benefits.

The report cites examples where treatment has benefited surrogate markers, but has harmed patients. It urged far more rigorous evaluation of how surrogate endpoints are used.

According to this evidence, most people taking long term statins for primary prevention do not benefit. The magnitude of benefit is extremely small for those at low risk.

A radical restructuring of the normal and the pathological emerged in the second half of the 20th century. Symptomless persons at risk of future disease were increasingly classified as having medical conditions. Drug companies and their latest products have helped to shape and expand new risk based conditions—including high BP, type-2 diabetes and high cholesterol. Pharmaceuticals

played a central and active role in the definition of these categories of illness. The process to include people previously considered healthy could be seen as medicalization.

A major rethink of the role of surrogate endpoints in medicine is timely. Routinely approving and prescribing therapies on the basis of their effects on someone's numbers, rather than their health, is increasingly seen as irresponsible and dangerous.

Even when evidence supports some clinical benefits of popular "preventive" medicines for those at lower risks, a rational assessment reveals that many people must be treated to prevent one adverse event, so most users gain no direct benefit despite years of treatment.

Understanding biological mechanisms and diagnosing by numbers has undoubtedly brought benefits. Yet, as the definition of medical conditions expands via the relationship between science and the business of health care, this approach is conferring multiple medical labels on vast numbers of healthy people, who are then treated with preventive drugs that will not help most of them, and may hurt many.

See the full abstract for a more detailed account of this important article.

Most primary care clinicians would agree that many patients are drug-over-treated, especially the elderly. And often at the end of life. Anxiety and bother are increased as well as costs.

When assessing the benefit/harm-cost ratio of a drug, always calculate the absolute effects on outcomes—clinical outcomes if possible Do not depend on relative risk reductions of hazard ratios when assessing the clinical benefits of a drug.

Consider possible drug industry bias and "spin". This is common.

How should primary care clinicians respond to this problem? First, I believe the benefit /harm-cost of the drug should be estimated for the individual patient. Admittedly, this is a clinical judgment call. Second, discuss the possible benefits, harms, and cost of treatment with the patient, asking if they are acceptable. Much depends on personal choice. Always suggest a no-cost, safe alternative—lifestyle changes.

Do not use the "latest" drug because it seems better. Wait a few years to determine adverse effects. Think carefully before prescribing a long-term expensive drug for a patient at low risk.

Remember that the "target" is arbitrary. There is nothing magic about a target. Individual patients may benefit from less stringent outcomes. Reducing systolic BP from 160- to 150 will benefit, as will reducing LDL-c from 150 to 140, and BMI from 35 to 32. Benefit increases if several risk markers are treated simultaneously.

If you are gung ho to reach the target, and your patient's systolic is 145, and he is already taking one or two antihypertension drugs, I believe adding another will harm more than benefit.

This is not to state that there is no value in determining and acting on substitute endpoints. I believe they have benefited many patients. They should be used with some restraint. They may be the best evidence we have.

1 Google: Institute of Medicine Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease.

Substantial Reductions In Mortality Can Occur Within Months

8-2 MORTALITY FALLS RAPIDLY AFTER RISK-FACTOR CHANGE IN POPULATIONS

How quickly might benefits follow improvements in risk factors in entire populations.? Many investigations have assumed that this lag might be several decades. Indeed, the development of atherosclerosis—the underlying pathological process preceding most coronary and stroke events—normally takes many decades to progress. Aortic stiffening can be shown in obese children. Aortic fatty streaks are visible in some teenagers and young adults. Yet most cardiovascular events occur only after the age of 60.

Thus, the perception is that the process is of one that builds slowly over decades and that will reverse slowly, if at all.

This perception is wrong. Extensive empirical and trial evidence shows that substantial reductions in mortality can occur within months of smoking-cessation and within 1-3 years of dietary changes. This reduction applies to both individuals and to entire populations.

Examples:

After the city of Helena, Montana introduced smoke-free legislation in 2002, admissions for acute coronary syndromes fell by 40% within 6 months. However, the law was rescinded, and coronary admissions returned to past levels within 6 months.

Similar smoke-free legislations in Scotland in 2006 was shortly followed by a 17% decrease in hospital admissions and a 6% decrease in out-of-hospital cardiac deaths.

Randomized trials show that changes in diet can rapidly improve outcomes of cardiovascular disease. A study of over 2000 survivors of myocardial infarction who were advised to eat fatty fish had a 29% reduction in all-cause mortality compared with control patients. The survival curves separated within a few months. Another trial of over 1100 patients with cardiovascular disease

randomly assigned to supplements of n-3 polyunsaturated fatty acids vs controls, found that survival curves diverged early after randomization. Total mortality was significantly reduced after 3 months and cardiovascular deaths were reduced within 6 months.

Mortality rates for coronary artery disease(**CAD**) rose steadily during the 20th century, peaking in 1970s and 1980s. However, in the early 1940s (during world war II) a reduction in mortality was observed in Holland and Norway. This was attributed to the decreased intake of meats and animal fats because of rationing and starvation. (*Prevalence of type-2 diabetes also fell dramatically Ed.)*

Poland became democratic in 1989. Rates of CAD mortality fell steeply by 25% in the next 5 years. This was attributed to the loss of communist subsidies for meat and animal fats and the influx of cheap vegetables, oils and fruits.

In Cuba, the gross domestic product fell by 80% after the Russian economic collapse in 1991. The crisis lasted until 1995, during which period caloric intake per person fell by 36% and the lack of public transportation led to increased physical activity Mean population weight fell by 1.5 units of BMI. Rates of coronary death fell by 39%.

These associations are not necessarily causal. Natural experiments can permit only ecological analysis. However, the findings are consistent with extensive causal evidence from laboratory studies and randomized trials.

The lag between improvement in risk factors and corresponding decreases in cardiovascular mortality has traditionally been perceived in terms of decades. However, evidence from clinical trials and natural experiments suggests a new paradigm. Substantial declines in mortality happen rapidly after individual or population-wide changes in diet or smoking.

The message is clear. Policy interventions which achieve population-wide changes such as smoke-free legislation, or reductions in dietary salt, trans fats, or saturated fats, can be effective and cost-saving and could achieve substantial and surprisingly rapid reductions in disease.

Lancet August 27, 2011;378: 752-53 Commentary first author Simon Copewell, University of Liverpool, Liverpool, UK

I abstracted this article to inform individuals contemplating life-style changes that benefits ensue quickly. This may be encouraging and increase compliance.

The article presents a figure of age-adjusted rates of ischemic heart disease in the US during the periods 1986-2002. For men, mortality fell from about 450 per 10000 in 1986 to about 225 per 10000 in 2002. This was likely due, in part, to improvements in prevention.

"Advocating For Just And Cost-Effective Distribution Of Finite Clinical Resources".

8-3 THE "TOP 5" LIST IN PRIMARY CARE: Meeting the Responsibility of Professionalism

Physicians can adhere to the principles of professionalism by practicing high-quality, evidence-based care and advocating for just and cost-effective distribution of finite clinical resources.

To promote these principles, The National Physicians Alliance (**NPA**) initiated a project "Promoting Good Stewardship in Clinical Practice"

NPA was formed to develop and disseminate lists of evidence-based, quality-improving, resource-sparing activities that could be incorporated into the practices of primary care medicine (pediatrics, family medicine and internal medicine).

Each activity was to be well supported by evidence, have beneficial effects on patient-health by improving treatment and/or reducing risk, and where possible, reducing costs of care.

The focus was on the top 5 examples of the most egregious causes of waste the medical profession could demonstrate to a skeptical and concerned public that high-quality care and efficient use of resources are complementary.

The top 5 in internal medicine recommend more thoughtful consideration of:

1) Low-back imaging
2) Blood chemistry screening
3) Routine ECGs
4) Routine use of generic statins vs more expensive statins
5) Use of dual X-ray screening for osteoporosis

Family medicine adds two:

6) Routinely prescribing antibiotics
7) Pap tests

Misunderstanding and misconceptions between physician and patients explain a significant part of why unnecessary and even harmful tests and treatments are ordered. Many primary care clinicians state that pressure from a patient leads them to prescribe antibiotics when they are not indicated. Yet studies have shown that, in fact, patients do not expect antibiotics nearly as often as doctors believe.

Patient's satisfaction and understanding are closely related. Physicians can improve patient satisfaction by focusing on understanding. This can be achieved by acknowledging and validating patient concerns while providing factual information in an easy-to-understand manner, explicitly clarifying the rational for a selected course of action, and providing a contingency plan that empowers the patient.

Please see the full abstract for details.

I believe primary care clinicians do over-prescribe and over-screen. Their message is "think twice before prescribing thee interventions".

I hope the NPA continues to publish more on this subject. The recommendations, however, are based on generalities (a population). Primary care is based on specifics (a patient). There is a major difference. Primary care clinicians often do deal with patients who demand a certain intervention. As the article states, the approach then is to carefully explain and instruct. When you are reluctant to prescribe antibiotics for sore throat or bronchitis, explain the reasons carefully and stress that antibiotics have harms as well as benefits.

There are situations where patients' anxiety is relieved by a prescription or a screening intervention. We could argue that relief of anxiety is a major responsibility of primary care.

Regarding antibiotics for sorer throat and bronchitis, I still fall back on the "if" or the "delayed" prescription. After explaining pros and cons of the antibiotic, if the patient insists, give him a prescription with the admonition not to have it filled for a few days, waiting for symptoms to calm. If symptoms persist or worsen, fill the prescription. This gives the patient some control. Most of the time it will not be filled. This avoids a second office visit or a follow-up telephone call.

Accounts For Half Of The Cases Of Congestive Heart Failure

8-4 PROGRESSION OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND RISK OF HEART FAILURE

Heart failure (**HF**) may develop with *reduced* left ventricular ejection fraction (**LVEF**) or with *preserved* LVEF.

Each form accounts for about half of cases.

Heart failure due to diastolic dysfunction (**DD*)*** is usually defined as HF with preserved LVEF. It is highly prevalent. (S*ystolic* HF is defined as LVEF less than 50%)

Approximately 7% of persons over age 45 have moderate to severe diastolic dysfunction, most of whom report few, if any, symptoms.

This study measured changes in diastolic function over time to identify factors predicting a change in diastolic function, and to determine the relationship between diastolic function and risk of subsequent HF.

Examination 1 (1997-2000): Randomly selected 2042 population-based persons age 45 and older for clinical examination and echocardiography.

Examination 2 (2000-2004): Examined and performed repeat echocardiography on 1402 persons from preceding cohort for follow-up.

The study focused on the period after examination 2 (2004-2010; n = 1358) following the cohort passively to ascertain the incidence of HF.

Diastolic function:

Measured diastolic function by 2-dimentional Doppler echocardiography.

Diastolic dysfunction was assessed by Doppler examination of *velocity* of flow across the mitral valve and pulmonary veins.

Flow into the ventricle normally varies during different times of diastole. (Early, when the mitral valve first opens. And late, when flow increased due to Atrial contraction.) The study calculated the E:A ratio at various times during diastole.

Depending on changes in function during different stages of diastole, the ratio of E:A changes. Depending on the types of change, diastolic dysfunction can be classified as mild, moderate, and severe.

Regardless of changes in left ventricular volume and pressure during diastole, the ejection fraction from ventricle remained "normal"—ie, greater than 50%. (*However, the minute-volume of blood ejected is decreased and HF eventually occurs. Ed.)*

During the 6 years of additional follow-up:

	Heart failure	
	Yes	No
Number (%)	81 (%)	1272
Age (y)	75	64
Hypertension (%)	78	40
Diabetes (%)	23	10
Coronary disease (%)	38	14

There was a marked progression DD: 23% of participants showed worsened diastolic function.

Heart failure occurred in 2.6% of those with normal diastolic function; in 8% of those who progressed to mild diastolic dysfunction; and in 12% of those with moderate or severe diastolic dysfunction.

Incident HF during the final 6 years of follow-up was associated with hypertension, diabetes, coronary heart disease, diastolic dysfunction, and especially age.

The biological pathway of DD leading to HF with preserved LVEF is still debatable. Contributing factors include changes in myocardial relaxation and elastic recoil, changes in ventricular load, diastolic stiffness, and external constraint. Age-related change in peripheral vascular elasticity and its effect on left ventricular load and stiffness may play an important role in the process.

To put DD into context, it should be noted that only about 1 in 4 persons with severe DD in examination 2 developed incident HF in long-term follow-up. This suggests that clinical events superimposed on DD play an important role in the transition from asymptomatic DD to over HF with preserved ejection faction.

Prevention of risk factors, especially hypertension, might be fundamental to reducing HF with preserved LVEF.

Conclusion: Left ventricular DD is associated with aging. It is highly prevalent and tends to worsen over time. Worsening DD can be detected in apparently healthy persons.

"Our data suggest that persistence or progression of diastolic dysfunction is a risk factor for heart failure in elderly persons."

This is a complex study. I struggled to abstract it concisely and accurately.

I abstracted it mainly to learn more about diastolic function and HF.

I still do not fully comprehend the Doppler measurements of velocity flow into the ventricle. I believe it would require several at-hand demonstrations.

The importance of the message is that DD and diastolic HF are very common; and that there are interventions that may reduce its incidence and severity . While we can do nothing about ageing, we can prevent and control hypertension, diet, lipids, diabetes, and other classical risk factors for HF.

Should Be Considered A Routine Screening Test

8-5 HAS THE TIME COME TO INCLUDE URINE DIPSTICK TESTING IN SCREENING YOUNG ADULTS?

Isolated microscopic hematuria may be detected incidentally in asymptomatic young adults by dipstick test (for heme[1]) and confirmed by microscopy. Microscopic hematuria may be transient. It has a widely variable prevalence range. Even when microscopic hematuria persists, further evaluation may fail to find the cause. This is often termed isolated "benign hematuria".

A study in the August 17, 2011 issue of JAMA describes a group of over 1 199 000 asymptomatic young adults, in whom 3 out of 1000 had persistent isolated microscopic hematuria.

(PIMH) It was not clear how many of those with microscopic hematuria also had proteinuria (micro-albunimuria).

During a 22 year follow-up, end-stage kidney disease (mainly glomerular disease) developed in 0.70% of this group. ESKD also developed in 0.04% of those without PIMH.

PIMH was a strong predictive risk marker for ESKD. It was much more common in those with PIMH than in those without—19 times more common.

In the US, chronic kidney disease (**CKD**) is estimated to be 70 to 200-fold more prevalent than treated end stage kidney disease (**ESKD**). An argument could be made for including dipstick testing for hematuria as part of the routine workup. A stronger case could be made for simultaneously detecting unsuspected proteinuria—defined as micro-albunimuria by albumin/creatinine ratio of 30 to 300 mg per gram. Proteinuria is associated with increased risk of cardiovascular and all-cause mortality as well as development of CKD.

A study from Canada, including more than 920 000 individuals, found that prevalence of dipstick positive proteinuria of trace or 1+ was 8%. This was associated with a hazard ratio of 2 for all-cause mortality and 3 for doubling of serum creatinine and 2 for ESKD among individuals with initially normal glomerular filtration rate. (**GFR**)

In a meta-analysis of over 1 million individuals, dipstick proteinuria of trace or greater was found in 8% of the cohort. This was associated with increased all-cause mortality, even among those younger than 65 with normal estimated GFR.

A study in Taiwan reported that the hazard ratio (**HR**) of dipstick proteinuria of trace or 1+ for all-cause mortality was comparable to the HR of smoking.

Proteinuria and micro-albunimuria are modifiable risk factors for which therapies are available to improve risk of CKD and cardiovascular disease. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers may reduce the relative risk of the composite end point of ESKD, doubling of serum creatinine, or death, by up to 40% in patients with non-diabetic nephropathy with proteinuria, and by up to 20% in those with diabetic nephropathy.

Early recognition of persons at risk for CKD should promote interventions for smoking cessation, hypercholesterolemia, glycemic control, and reduction in sodium intake.

It appears that the time may have arrived for routine dipstick screening at least at initial examinations and perhaps every 5 years thereafter.

In the "olden days" when I first entered the profession, the chart was not complete if it did not contain an urinalysis. Urinalysis was more complicated at the time. Separate tests for glucose and albumin were required, as well as microscopy.

The dipstick made things much simpler. It has some benefits as a screening test: Available at point-of-contact; fast; easily and immediately interpreted; and low cost. (A dipstick can be obtained for less than 50 cents.)

I suspect that proteinuria is more common than hematuria.

Preventive treatment is now available, including efforts to reduce risk of cardiovascular disease.

For another commentary on proteinuria, see Practical Pointers January 2011.

FULL ABSTRACTS AUGUST 20011

"We Need A New Approach To Proxy Measures Of Health."

8-1 SURROGATES UNDER SCRUTINY

We live in a time when disease is measured *not* by symptoms, but by numbers determined by biomarkers. Transferring a healthy person's risk of disease into a chronic condition has become a key characteristic of modern medicine, creating vast new markers for "preventive" pills designed to reduce suffering and extend life.

Well funded campaigns urge the public to "know your numbers" and "treat to target".

But the grand assumption underlying this approach—that helping patients' numbers will automatically improve their health—is a delusion as dangerous as it is seductive.

For example:

Long term hormone replacement therapy, which lowered "bad" cholesterol and raised "good" cholesterol for generations of women, actually increased risk of stroke and heart attacks.

Drugs to aggressively reduce blood glucose in diabetes patients increased risk of premature death rather than reducing it.

Use of flecanide to reduce the number of irregular heart beats raised the risk of an early death.

Since the 1950s, studies show correlations between high BP and heart disease. This led to the belief that, if we can modify biomarkers, we can lower risk of death and disease. While this sometimes works, its logical flaw is obvious. Whether we help or harm depends on how we lower risk—and long term treatments often carry unintended consequences. Even when significant clinical benefits are proved, the often minimal risk reductions associated with long term treatment suggest that the current approach may be over-medicating for little gain at great cost.

Unproved benefits:

We have been too eager to accept favorable changes in biomarkers as a proxy for patient benefit. The focus on "knowing your numbers" and "treat to target" has seemed to be in everyone's best interest—it is an easy public health message, it requires only quick visits to the doctor. They are a boon for drug companies that do not have to do the large, long term studies of effects on clinically meaningful outcomes.

Simple assumptions about surrogate outcomes are often incorrect. We need to better inform patients about potential harms. If a drug is approved only on the evidence of its impact on a biomarker, there should be clear warnings that it has unproven effects on patient health.

Report from the Institute of Medicine: (**IOM**)

The IOM recently issued *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease.*[1] It is sobering. It details the often misplaced confidence when relying on surrogate endpoints to assess treatment benefits. Cautionary voices speaking about the risks of using surrogate endpoints have been repeating the same messages for 20 years. The report cites examples where treatment has benefited surrogate markers, but has harmed patients. It urged far more rigorous evaluation of how surrogate endpoints are used.

Even for widely used surrogate endpoints, there is more uncertainty than we might imagine. Even though BP is an extremely reliable proxy, questions arise from the fact that treatments that have similarly affecting BP can have different effects on heart disease.

In the face of the AIDS crisis, researchers discovered HIV-RNA was a biomarker enabling experimental drugs to be assessed quickly. However, short term changes in that biomarker proved to be a poor surrogate because partial suppression of the virus allowed for the formation of drug resistant mutations and limited the future usefulness of drugs.

Although reduction in tumor size is sometimes a useful way to measure effects of cancer treatment, even major shrinkage does not always represent meaningful improvement because, in some cancers, smaller tumors grow faster than larger tumors.

Caution over cholesterol:

There are many uncertainties about cholesterol.

Regulators, including the FDA, have officially sanctioned low density lipoprotein cholesterol (**LDL-c**) as a surrogate endpoint, allowing many drugs to be approved without requiring proof that they will improve health.

Although the methods used to determine blood cholesterol are reliable and reproducible, they do not directly measure LDL-c. Some have limitations.

Although LDL-c has been hypothesized to have a causal role in atherosclerotic disease, it has not been conclusively proven. "Lowering LDl cholesterol does not always correlate with improved patient outcome." There are many coronary risk factors, and cholesterol, while currently considered by many to be a valuable biomarker for heart disease, is only one of them.

The benefits of long term preventive therapies like cholesterol lowering drugs are usually portrayed as relative risk reductions. When considered in absolute terms, a different picture emerges.

In a Cochrane review of trials for primary prevention in people without a history of heart disease, statins reduced premature death, coronary heart disease, stroke, and revascularization variously by 17% to 34%. In absolute terms, over 4 to 5 years, reductions were between 0.5% and 1.8%. The estimated number needed to treat to prevent one event ranged from 50 to 200. According to this evidence, most people taking long term statins for primary prevention do not benefit. The magnitude of benefit is extremely small for those at low risk,

There is also a question of the effect of industry funding on the evidence. Even small amounts of bias could make a difference between a finding of benefit and a finding of no effect.

There is cause for great caution in interpreting the existing evidence of statins for primary prevention, questioning the benefits of long term preventive medication for otherwise healthy individuals.

Caution about trials of statins: The Cochrane reviewers were unable to disaggregate composite outcome measures reported in 14 statin trials. The majority of trials did not mention possible harms. Two trials were stopped prematurely. This may lead to an overestimation of treatment effects. All but one of the trials had some form of industry sponsorship, which has been shown to increase the likelihood of bias.

A radical restructuring of the normal and the pathological emerged in the second half of the 20th century. Asymptomatic persons at risk of future disease were increasingly classified as having medical conditions. Drug companies and their latest products have helped to shape and expand new risk based conditions—including high BP, type-2 diabetes and high cholesterol. Pharmaceuticals played a central and active role in the definition of these categories of illness. The process to include people previously considered healthy could be seen as medicalization.

The relationship between business and science is evident in the more recent development of "quality measures", which urges doctors to test for and treat the risks based conditions of health. *The National Committee for Quality Assurance* is directly funded by several drug companies.

A major rethink of the role of surrogate endpoints in medicine is timely. Routinely approving and prescribing therapies on the basis of their effects on someone's numbers, rather than their health, is increasingly seen as irresponsible and dangerous.

Even when evidence supports some clinical benefits of popular "preventive" medicines for those at lower risks, a rational assessment reveals that many people must be treated to prevent one adverse event, so most users gain no direct benefit despite years of treatment.

Understanding biological mechanisms and diagnosing by numbers has undoubtedly brought benefits. Yet, as the definition of medical conditions expands via the relationship between science and the business of health care, this approach is conferring multiple medical labels on vast numbers of healthy people, who are then treated with preventive drugs that will not help most of them, and may hurt many.

BMJ August 20-27; 343: 399-401 Editorial by Ray Moynihan, University of New Castle, Australia.

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"Advocating For Just And Cost-Effective Distribution Of Finite Clinical Resources".

8-3 THE "TOP 5" LIST IN PRIMARY CARE: Meeting the Responsibility of Professionalism

Physicians can adhere to the principles of professionalism by practicing high-quality, evidence-based care and advocating for just and cost-effective distribution of finite clinical resources.

To promote these principles, The National Physicians Alliance (**NPA**) initiated a project "Promoting Good Stewardship in Clinical Practice"

NPA was formed to develop and disseminate lists of evidence-based, quality-improving, resource-sparing activities that could be incorporated into the practices of primary care medicine (pediatrics, family medicine and internal medicine).

Each activity was to be well supported by evidence, have beneficial effects on patient-health by improving treatment and/or reducing risk, and where possible, reducing costs of care.

The focus was on the top 5 examples of the most egregious causes of waste the medical profession could demonstrate to a skeptical and concerned public that high-quality care and efficient use of resources are complementary.

RESULTS

1. The lists were completed after several rounds of debate.

2, The top 5 for internal medicine:

1) Do not do imaging for low back pain within the first 6 weeks unless red flags are present.

- Imaging of the lumbar spine before 6 weeks does not improve outcomes. It increases costs.
- Red flags: Severe or progressive neurological deficits or when serious underlying conditions

(eg, osteomyelitis) are suspected. Source: Cochrane collaboration..

2) Do not obtain blood chemistry panels (eg, baseline metabolic panel) or urinalysis for screening asymptomatic healthy adults.

- Only lipid screening yields significant numbers of positive results among asymptomatic patients.
- Screen for type-2 diabetes in adults with hypertension. Source: USPSTF.

3) Do not order annual ECGs or any other cardiac screening for asymptomatic low-risk patients

- Little evidence that detection of coronary artery stenosis in asymptomatic patients at low risk for CHD improves health outcomes.
- False-positive tests are likely to lead to harm through unnecessary invasive procedures, overtreatment and misdiagnosis.
- Potential harms of routine annual screening exceed the potential benefits. Source: USPSTF

4) Use only generic statins when initiating long-term drug therapy

- All statins are effective in lowering mortality, heart attacks, and stroke when dose is titrated to affect appropriate LDL-c reduction.
- Switch to a more expensive brand-name statin only if a generic statin causes clinical reactions or does not achieve LDL-c goals. Source The MERCURY Trial

5) Do not use DEXA screening for osteoporosis in women under age 65 or men under 70 with no risk factors

- Not cost-effective in younger, low-risk patients, but cost effective in older patients
- Risk factors include, but are not limited to, fracture after age 50, prolonged exposure to corticosteroids, diet deficient in calcium or vitamin D , cigarette smoking, alcoholism, and thin and small build. Source:. USPSTF,

2. For family medicine: low back imaging, annual ECG, and DEXA screening were also included. Two were different:

6) Do not routinely prescribe antibiotics for acute mild-to-moderate sinusitis unless symptoms (which must include purulent nasal secretions AND maxillary pain or facial or dental tenderness to pressure) last for 7 or more days OR if symptoms worsen after initial clinical improvement.

- Most maxillary sinusitis in the ambulatory setting is due to viral infection that will resolve on its own
- Despite consistent advice to the contrary, antibiotics are prescribed in over 80% of outpatient visits for acute sinusitis
- Sinusitis accounts for 16 million office visits and $5.8 billion in annual healthcare costs. Source: Cochrane

7) Do not perform Pap tests on patients younger than 21 years, or in women status post-hysterectomy for benign disease.

- Most dysplasia in adolescents regresses spontaneously, therefore, screening PAP tests done in this age group can lead to unnecessary anxiety, morbidity, and cost.
- Pap tests have low yield in women after hysterectomy for benign disease, and therefore is poor

evidence for improving outcomes. Source: USPSTF

(I omit the pediatric recommendations. Ed.)

DISCUSSION

1. Physician panels in primary care identified common clinical activities that could lead to higher-quality care and better use of finite clinical resources.
2. Field testing show support among physicians for the evidence supporting these recommendations, the potential positive impact on quality and costs, and the ease with which the recommendations could be implemented.
3. Successful implementation would depend on enlisting patient agreement with the recommendations.
4. Misunderstanding and misconceptions between physician and patients explain a significant part of why unnecessary and even harmful tests and treatments are ordered. Many primary care clinicians state that pressure from a patient leads them to prescribe antibiotics when they are not indicated. Yet studies have shown that, in fact, patients do not expect antibiotics nearly as often as doctors believe.
5. Patient's satisfaction and understanding are closely related. Physicians can improve patient satisfaction by focusing on understanding. This can be achieved by acknowledging and validating patient concerns while providing factual information in an easy-to-understand manner, explicitly clarifying the rational for a selected course of action, and providing a contingency plan that empowers the patient.
6. Patient-centered approaches that discuss expectations and share information with patients have been shown to successfully reduce antibiotic prescriptions in primary care.
7. NPA plans to request the endorsements of consumer groups and patient safety groups for the recommendation of the top 5. This will help dispel the misconception that these clinical recommendations represent rationing and support the idea that often "less is more".

Archives Internal Medicine August 8/22 2011 by The Good Steward Working Group.
Correspondence to Stepheh_R_Smith@brown.edu

Accounts For Half Of The Cases Of Congestive Heart Failure

8-4 PROGRESSION OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND RISK OF HEART FAILURE

There is an emerging emphasis on understanding the progress from risk factors for heart failure (**HF**) to asymptomatic ventricular dysfunction and eventually to symptomatic HF and death.

It is important to have population-based information on changes in cardiac function over time.

HF increases with advancing age.

HF may develop with *reduced* left ventricular ejection fraction (**LVEF**) or with *preserved* LVEF.

Each form accounts for about half of cases.

Heart failure due to diastolic dysfunction (**DD*)*** is usually defined as HF with preserved LVEF. It is highly prevalent. (S*ystolic* dysfunction is defined as LVEF less than 50%)

Little is known about time-dependent changes in diastolic function or their relationship to clinical HF.

The objective of this study was to measure changes in diastolic function over time, to identify factors predicting a change in diastolic function, and to determine the relationship between diastolic function and risk of subsequent HF.

Participants:

Examination 1 (1997-2000): Randomly selected 2042 population-based persons age 45 and older for clinical examination and echocardiography.

Examination 2 (2000-2004): Examined and performed repeat echocardiography on 1402 persons from preceding cohort for follow-up.

Incident HF between examinations 1 and 2 was diagnosed by the Framingham criteria. Also determined incidence of diabetes, hypertension, and myocardial infarction.

After examination 2, (2004-2010 n = 1277) the cohort was followed passively to ascertain the incidence of HF.

Echocardiography:

Measured diastolic function by 2-dimentional Doppler echocardiography.

Diastolic dysfunction was assessed by Doppler examination of *velocity* of flow across the mitral valve and pulmonary veins. Impaired flow into the ventricle varies during different times of diastole. (Early, when the mitral valve first opens. And late, when flow was increased due to Atrial contraction .) The study calculated the E:A ratio at various times during diastole.

The degree of impaired inflow can be designated as mild, moderate, and severe depending on various changes in the ratio between velocity of Early and Atrial inflow. (The E:A ratio)

The late (Atrial boost) inflow is absent when atrial fibrillation occurs.

Ventricular pressures and volumes can be estimated during various phases of diastole.

Regardless of changes in left ventricular volume and pressure during diastole, the ejection fraction from ventricle remains "normal"—ie, greater than 50%. *(However, the minute-volume of blood ejected is decreased and HF eventually occurs. Ed.)*

RESULTS

1. Characteristics (means over 4 years; n = 1402) of participants; examination 1 and 2: TABLE 1

	Exam 1 (1997-2000)	Exam 2 (2000-2004)
Age	61	65
Hypertension (%)	26	42
Diabetes (%)	6	10
Coronary disease (%))	11	16
HF (%)	1	2
LVEF (%)	64	66
Diastolic function (%)		
Normal	70	49
DD any severity	21	32
(Not determined in many subjects)		

2. Changes in diastolic function in *healthy* subjects over 4 years:

At baseline, over 500 participants were *without* hypertension, coronary artery disease, and diabetes, HF, or use of cardiovascular medications

Incidence of DD increased from 11% to 30%

Prevalence of elevated filling pressure increased from 17% to 45%.

4. Baseline factors predictive of incident HF after exam 2 (2004-2010) :

	HF	No HF
Number	81 (6%)	1272
Age (mean)	75	64
Hypertension (%)	73	40
Diabetes (%)	23	10
Coronary disease (%)	38	14
DD (%)	75	43

During the 6 –years of additional follow-up, heart failure occurred in 2.6% of those with normal diastolic function; in 8% of those who progressed to mild diastolic dysfunction; and in 12% of those with moderate or severe diastolic dysfunction.

DISCUSSION

1. Approximately 7% of persons over age 45 have moderate to severe diastolic dysfunction, most of whom report few, if any, symptoms.
2. There was a marked progression DD: 23% of participants showed worsened diastolic function over 10 years.
3 A similar pattern of worsening diastolic function was observed in a subset of healthy participants. This may support the concept that aging per se may be accompanied by progressive deterioration in diastole function.
4. Incident HF during the final 6 years of additional follow-up was associated with age, hypertension, diabetes, coronary heart disease, and diastolic dysfunction.
5. The biological pathway of DD leading to HF with preserved LVEF is still debatable. Contributing factors include changes in myocardial relaxation and elastic recoil, changes in ventricular load, diastolic stiffness, and external constraint. Age-related change in peripheral vascular elasticity and its effect on left ventricular load and stiffness may play an important role in the process.
6. This population-based study found that incidence of HF related to *systolic* dysfunction remained constant over the years, but HF due to *diastolic* dysfunction increased.
7. To put DD into context, it should be noted that only about 1 in 4 persons with severe DD in examination 2 developed incident HF in long-term follow-up. Clinical events superimposed on DD may play an important role in the transition from asymptomatic DD to over HF with preserved ejection faction.
8. Prevention of risk factors, especially hypertension, might be fundamental to reducing HF with preserved LVEF.

CONCLUSION

Left ventricular DD is associated with aging. It is highly prevalent and tends to worsen over time.

Worsening DD can be detected in apparently healthy persons.

“Our data suggest that persistence or progression of diastolic dysfunction is a risk factor for heart failure in elderly persons.”

JAMA August 24-31; 306: 856-64

Original investigation by The Olmstead County Heart Function Study. first author Garvanp C Kane, Mayo Clinic, Rochester Minn. . (Olmstead county Minn. is the home of the Mayo clinic.)

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Should Be Considered A Routine Screening Test

8-5 HAS THE TIME COME TO INCLUDE URINE DIPSTICK TESTING IN SCREENING YOUNG ADULTS?

Urinalysis was once a standard test in routine health evaluation. Recently, it has not been advised for healthy individuals under age 60 unless they are at high-risk for kidney or cardiovascular disease.

The dipstick is a simple and inexpensive means of detecting unsuspected hematuria and proteinuria.

Isolated microscopic hematuria may be detected incidentally in asymptomatic young adults by dipstick test (for heme[1]) and confirmed by microscopy. Microscopic hematuria may be transient. It has a widely variable prevalence range. Even when microscopic hematuria persists, further evaluation may fail to find the cause. This is often termed isolated "benign hematuria". Renal biopsy is usually not considered helpful. Long term prognosis is not known.

A study in this issue of JAMA[2] describes a group of over 1 199 000 asymptomatic young adults, in whom 3 out of 1000 had persistent isolated microscopic hematuria. (**PIMH**) It was not clear how many of those with microscopic hematuria also had proteinuria (micro-albunimuria).

During a 22 year follow-up, end-stage kidney disease (mainly glomerular disease) developed in 0.70% of this group. ESKD also developed in 0.04% of those without PIMH.

PIMH was a strong predictive risk marker for ESKD. It was much more common in those with PIMH than in those without—19 times more common.

What should the clinician do when the dipstick test for blood is positive?

Confirm by finding 2 to 5 or more red blood cells per high-power field by microscopy of the urinary sediment on at least two occasions. The finding of acanthocytic RBC, or RBC casts would suggest a glomerular source.

Concomitant proteinuria and elevated serum creatinine would also suggest glomerular disease.

Such patients should be evaluated every1 to 2 years for possible increased incidence of proteinuria, hypertension, and renal insufficiency.

In the US, chronic kidney disease (**CKD**) is estimated to be 70 to 200-fold more prevalent than treated end stage kidney disease (**ESKD**). An argument could be made for including dipstick testing for hematuria as part of the routine workup. A stronger case could be made for simultaneously detecting unsuspected proteinuria—defined as micro-albunimuria by albumin/creatinine ratio of 30 to 300 mg per gram. Proteinuria is associated with increased risk of cardiovascular and all-cause mortality as well as development of CKD.

A study from Canada, including more than 920 000 individuals, found that prevalence of dipstick positive proteinuria of trace or 1+ was 8%. This was associated with a hazard ratio of 2 for all-cause mortality and 3 for doubling of serum creatinine and 2 for ESKD among individuals with initially normal glomerular filtration rate. (**GFR**)

In a meta-analysis of over 1 million individuals, dipstick proteinuria of trace or greater was found in 8% of the cohort. This was associated with increased all-cause mortality, even among those younger than 65 with normal estimated GFR.

A study in Taiwan reported that the hazard ratio (**HR**) of dipstick proteinuria of trace or 1+ for all-cause mortality was comparable to the HR of smoking.

The cost of confirming micro-albunimuria by albumin /creatinine ratio is modest.

Despite the increasing prevalence of CKD—estimated to be 14% in the US—relatively few patients are aware of the diagnosis.

Proteinuria and micro-albunimuria are modifiable risk factors for which therapies are available to improve risk of CKD and cardiovascular disease. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers may reduce the relative risk of the composite end point of ESKD, doubling of serum creatinine, or death, by up to 40% in patients with non-diabetic nephropathy with proteinuria, and by up to 20% in those with diabetic nephropathy.

Early recognition of persons at risk for CKD should promote interventions for smoking cessation, hypercholesterolemia, and glycemic control, and to reduced sodium intake.

The US Preventive Services Task Force has not yet recommended routine screening for CKD.

In Japan, routine urinalysis screening has been widespread since 1983 with an apparent decrease in ESKD from glomerulonephritis.

It appears that the time may have arrived for routine dipstick screening at least at initial examinations and perhaps every 5 years thereafter.

JAMA August 17, 2011; 306:764-65 Editorial by Robert S Brown, Beth Israel Deaconess Medical Center, Boston Mass.

1 Heme: A large heterocyclic organic compound. containing iron molecule in the center of a porphyrin ring. A component of hemoglobin.

2 "Persistent Asymptomatic Isolated Microscopic Hematuria In Israeli Adolescents And Young Adults And Risk For End-Stage Renal Disease" JAMA August 17, 2011; 306: 729-36 First author Assf Vivante, Israeli Defense Forces Medical Corps

This nation-wide retrospective populating-based study evaluated the risk of end-stage kidney disease in a cohort of over 1 200 000 inductees (age 16-25; 60% male; all Jewish) into the Israeli Army in 1975-97.

All were tested by dipstick for hemoglobin.

Determined incidence of persistent asymptomatic isolated microscopic hematuria (PIMH)in those positive.

Determined incident treated cases of end-stage kidney disease (ESKD) 1980-2010 in the cohort. (Defined as need for dialysis of renal transplant.)

PIMH was diagnosed in 0.3% of eligible individuals. (3690 of 1 203 626)

During 22 years of follow-up treated ESKD as related to incidence of PIMH:

Cohort with PIMH 26 of 3690 individuals (0.70%) 34 per 100 000 person-years.

Cohort without PIMH 539 of 1 199 936 individuals (0.045%) 2 per 100 000 person years.

A crude hazard ratio of 19.

PIMH was a strong marker for ESKD.

The fraction of treated ESKD attributed to microscopic hematuria was 4.3%.

Conclusion: PIMH in persons age 16-25 was associated with significantly increased risk of treated ESKD over a period of 22 years.

The incidence and absolute risk of ESKD was very low.

The age when ESKD developed must have been very young. The mean age at discovery of PIMH was about 20. The development of ESKD occurred over 22 years. This would place onset about age 42. .