JOURNAL OF INSURANCE MEDICINE

FROM THE ASSOCIATE EDITOR

Michael L. Moore

You will notice in this issue that the Literature Review has a slightly new look and focus. Like previous issues in which Dr Goldstone did such a marvelous job, this section will try to keep you up on the latest information appearing in the medical literature. However there will be a few differences. First, I will be joined by five other reviewers who will add their expertise to the column. I am pleased to have Keith Clark, M.D., A.C. Favors, M.D., Linda Goodwin, M.D., Wayne Heidenreich, M.D., and John Kirkpatrick, MD join me in this column. In addition to explaining what a particular article said, we will also try to point out what this really means in the face of other literature pieces or the state of the insurance industry. We hope you will enjoy this new format and find it helpful in your quest for information.

JOURNAL OF INSURANCE MEDICINE

LITERATURE REVIEW

Diabetes Mellitus

Keith Clark

Reference: Peters, A. L. et al. A Clinical Approach for the Diagnosis of Diabetes Mellitus: An Analysis Using Glycosylated Hemoglobin Levels. Journal of the American Medical Association, *1996, 276;* 1246-1252.

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Key Words: Diabetes Mellitus Glycosylated Hemoglobin

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This review article combined published individual data comparing oral glucose tolerance testing with glycosylated hemoglobin testing for the diagnosis of diabetes. Data was obtained from 31 studies, representing 13,628 subjects.

Although oral glucose tolerance testing (OGTT) is one of the basic standards for the diagnosis of diabetes mellitus (World Health Organization), it is not commonly used clinically except for gestational diabetes. OGTT may be a "gold standard" but it is expensive, subject to lack of testing compliance and is poorly reproducible. Fasting plasma glucose (FPG)>140 mg/dl on two occasions is the most widely used standard. HbA1c is widely used to guide the treatment of diabetes mellitus but not for diagnosis.

The study attempted to compare OGTT and HbA1c but "Due to lack of agreement between HbA1c levels and OGTT results, the HbA1c data was analyzed independent of the

HbA_{1c} Level Cutpoint	Sensitivity (% of diabetes Mellitus Subpopulation with HbA_{1c} above the cutpoint)	Specificity (% of Normal Glucose Tolerance Subpopulation with HbA_{1c} Level below the cutpoint)	% of Impaired Glucose Tolerance Subpopulation with HbA_{1c} Above the Cutpoint
5.5	100.0	69.1	79.0
6.0	100.0	90.9	64.2
6.5	100.0	98.5	46.8
7.0	99.6	99.9	30.1
7.5	98.9	100.0	16.7

OGTT findings". Basically, they discarded their direct comparison of HbA1c to OGTT.

They divided the subjects into three groups:

• **Normal Glucose Tolerance** FPG<6.4mmol/L (115 mg/dL) and 2-hour postdextrose value <7.8mmol/L (140 mg/dl)

• **Impaired Glucose Tolerance** (IGT) FPG 6.4-7.7mmol/L(115-139 mg/dL) and 2-hour post-dextrose value of 7.8-11.0 mmol/L (140-199 mg/dl)

• **Diabetes** FPG≥7.8 mmol/L (140 mg/dL) and a 2-hour postdextrose value≥11.1mmol/L (200 mg/dl).

These three groups were identified in the four largest studies and the sensitivity and specificity of HbA1c for their detection is outlined in the following table.

The authors conclude that fasting plasma glucose should be done as an initial screen for diabetes. If it is ≤6.4 mmol/L(115 mg/dL) no further testing is necessary. If the FPG is ≥7.8 mmol/L (140 mg/dL0, the individual likely has diabetes. A repeat FPG should be done to confirm the diagnosis, and HbA1c is used to guide treatment. For an intermediate FPG 6.4-7.7 mmol/L (116-139 mg/dL), the individual either has diabetes or IGT. In these individuals, a HbA1c of ≥7.0% indicates diabetes and HbA1c of 6.0%-6.9% may be diabetes or IGT.

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LITERATURE REVIEW

Cancer Mortality

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Reference: Cole P., Rodu B., Cancer Mortality Declines in the United States. Cancer, November 15, 1996, "Declining Cancer Mortality in the United States."

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Table 1

Cancer Proportional Mortality and Age-Adjusted Mortality Rates[a] by Cause and Year; US Total Population

Year	CPM%	All Causes	All Cancer	Lung Cancer	Other Cancer
1970	17	714	129.9	28.4	101.5
1980	21	586	132.8	36.4	96.4
1990	24	520	135.0	41.4	93.6
1991	24	514	134.5	40.8	93.4
1992	24	505	133.1	40.8	92.3
1993	23	513	132.6	40.1	91.8
1994	24	508	(132.1)[b] 131.5[c]	40.1	92.0
1995	23	503	(130.8)[b] 129.8[c]	39.8	91.0
1990-1995 Reduction					
Total[a]	———	17	4.2 [5.2][d]	1.6	2.6
Annual[a]	———	3.4	0.8 [1.0][d]	0.3	0.5
Annual(%)	———	0.7	0.6 [0.8][d]	0.7	0.5

CPM: cancer proportional mortality
[a]Deaths per 100,000 person-years (py)
[b]Mortality rates not age-adjusted
[c]Age-Adjusted mortality rates updated after submission
[d]Figures based on age-adjusted mortality rates updated after submission

(After Cole; Rodu[1])

Table 1 separates total cancer mortality into lung cancer mortality and "all other cancers". In 1990 the all cancer mortality peaked at 135 and has declined each year thereafter to 129.8 (this age adjusted rate was not available until after submission). This total fall in "all cancer mortality" of 5.2 deaths per 100,000 person-years translates to a yearly decline of 0.8% per year. Nearly one-third of the decline of "all cancer deaths" is due to the reduction in lung cancer mortality of 1.6 deaths per 100,000 py, and the other two-thirds is due to a decline in all other cancers.

As Seen in Table 1, the percentage of all cancer deaths [CPM or Cancer Proportion Mortality] peaked in 1990 and has stabilized over the last five years at 23%. The increase was thought to be due to aging of the population where most cancers occur, and to a decrease in deaths from cardiovascular and strokes.[1,2]

It is important to view the decline in cancer mortality from the perspective of all cause mortality. There continues to be a significant drop in overall mortality every decade beginning with 1970. From 1990 to 1995 the overall mortality declined from 520 to 503, a decline of 17 deaths per 100,000 person-years, for an annual decline of 3.4%

Lung Cancer Mortality

The major cause of cancer, especially lung cancer, is due to smoking. The mortality peaked in 1990 and has trended slightly downward for several years thereafter, until 1995 when there was a significant decline of 1.6 deaths per 100,000 py. Presently, the mortality for lung cancer is still very high.[3] And unfortunately, this present decline in total lung cancer mortality obscures the continued steep rise in lung cancer mortality for women.[3]

The Center for Disease Control Prevention has estimated that reductions in smoking have contributed to the reduction of other cancers by 0.4 deaths per 100,000 person-years from 1990 to 1995. The "all cancer mortality" rate began to decline when the mortality rate for lung cancer began declining in 1990. This downward trend for "all cancer mortality" began twenty years later than the declining rate for "other cancers", which began declining in 1970.

Sources of Cancer Mortality Rate Reduction

Table 2

Estimated Reduction in Cancer Mortality Rate by Source: U.S. Total Population: 1990 - 1995

Source	Reduction[a]
Reduced smoking	-2.0
Lung cancer(-1.6)	
Other cancer(0.4)	
Other prevention	-0.4
Reduced case fatality rate	-3.0
Total estimated	-5.4
Observed	-4.2[b] (-5.2)[c]
Discrepancy	-1.2[b] (-0.2)[c]

[a]Deaths per 100,000 person-years
[b]Reductions prior to updated mortality rates in Table 1
[c]Observed reduction after update in Table 1

(After Cole; Rodu[1])

Table 2 summarizes the sources of the estimated reduction in all cancer mortality rates of 5.4 deaths per 100,000 person-years.[1] Reduced smoking accounts for a decline of 2.0 deaths per 100,000 py. Reduced case fatality rates are thought to be due to early detection (with improved survival) and improved medical care, including preventative measures. The authors of this paper felt that the decline in cancer mortality would continue over the next twenty years (unless there is a surge in incidence rates), because of the effects of long term reductions in smoking and reduced exposure to other lifestyle carcinogens (alcohol, solar radiation, and some industrial agents). This decline will be enhanced by further advances in cancer screening, diagnosis, and treatment.

Summary

This important paper, with the accompanying editorial, on the decline of "all cancer mortality" can be viewed as a mixed blessing.[1,2] It is a small decline which began in 1990. There was no single big bang reduction, but a culmination of declining death rates for lung, prostate, and cervical cancer due to early detection, improved medical therapy, and patient education. Cancer is the second leading cause of death and is likely to remain so for a while.

Will the current downward trend in cancer mortality continue? Against the background canvas of a beginning decline in "all cancer mortality", looms the threat of increased cancer mortality rates as more of our populous ages (where the cancer rates are the highest), more adolescents and young people are smoking, and continued smoking by women in whom smoking cessation has not been very successful.[4] The individual medical director is still faced with the day to day decision of risk assessment of individual cancers at whatever stage they are detected.

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LITERATURE REVIEW

Coronary Artery Disease and Altering Risk Factors

Linda Goodwin

Reference: O'Keffe JH, Conn RD, Lavie CJ, and Bateman TM. The New Paradigm for Coronary Artery Disease: Altering Risk Factors, Atherosclerotic Plaques, and Clinical Prognosis. Mayo Clinic Proc 1996; 71:957-65.

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Determining the severity of coronary artery disease (CAD) has treatment and mortality implications. The traditional "gold standard" for measurement of severity has been the coronary angiogram. However, recent studies indicate that endothelial wall stability and plaque structure are more important in determining the risk of future cardiac events than are angiographic estimates of the degree of fixed-lesion stenosis. This article reviews the old and new paradigms for diagnosis and treatment of CAD.

Angiogram interpretation is imprecise, but is generally used to identify "significant" stenoses, i.e. those more than 50% to 70% narrowed. Revascularization with CABG or PTCA has been the treatment of choice, despite evidence that these modalities confer a longevity advantage only in select groups, e.g. severe left main or extensive three-vessel disease with LV dysfunction, or CAD with diabetes for CABG, and acute MI for PTCA.

Most catastrophic complications of CAD are due to acute coronary syndromes. Prospective, sequential angiograms in cases of unstable angina or MI, have found that only 12% to 15% of lesions responsible for acute coronary events were greater than 70%, and that almost two-thirds of the lesions were less than 50%.

Dysfunctional endothelium can cause rupture of plaques or stimulate platelet adhesion, which can result in acute coronary syndromes. Risk factors for endothelial dysfunction occur with or without fixed plaques, and include elevated oxidized LDL cholesterol levels, hypertension, diabetes, smoking and lack of estrogen in women. Normalization of endothelial dysfunction has been shown to occur within days to weeks of risk factor modification, and is most likely a major reason for the early clinical benefits seen after such changes, e.g. the substantial decrease in angina found after initiation of Pravastatin therapy.

Inflammation also plays a role in CAD. Evidence of a systemic inflammatory response, including increased C-reactive protein and other acute phase reactants, is usually present in unstable angina but not in cases of stable angina or normal coronaries. This is related in part to high levels of oxidized LDL.

Angiographically "tight" lesions are still prognostically important because they serve as markers for overall plaque burden, especially the angiographically "silent" but unstable lesions. However, tight lesions are less likely to be the source of an acute coronary event, probably due to the association of collateral vessels with chronically high-grade stenoses.

Stress thallium testing measures the functional (as opposed to merely anatomic) component of CAD, and has been shown to be a more accurate means of predicting acute cardiac events than coronary angiography.

Dramatic reductions in coronary events, and in cardiac and all cause mortality, have been shown in aggressive lipid-lowering studies, even in patients with "normal" lipid levels, despite very minimal changes in the degree of stenosis of coronary lesions. There is increasing evidence that the beneficial cardiovascular effects of estrogen are related to stabilization of endothelial dysfunction, and it is of value even in elderly women with extensive CAD. The effects of hypertension control may relate to decreasing shear-forces on vulnerable plaques with thin over-lying or inflamed endothelium and high oxidized LDL-rich content.

Revascularization is of value in high risk patients, but risk factor modification will play an increasing role in the acute and chronic treatment of CAD in the future.

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LITERATURE REVIEW

Antinuclear Antibody Testing

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Reference: Slater CA, et al. Antinuclear Antibody Testing. Ach. Intern. Med. 1996 Jul 8; 156:1421-1425.

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This study's objective was to determine the clinical utility of ordering an ANA test to diagnose systemic lupus (SLE) and other rheumatic disease processes. It was based on a retrospective chart review of 306 patients drawn from 979 consecutive ANA tests at Beth Israel Hospital in Boston, Mass. The patients included both outpatients and inpatients and were cared for by both primary care and referral-based practices.

The study's diagnoses and prevalence of rheumatic diseases was based on the review of histories documented within several months of the ANA test results. The top three indications for testing were suspected rheumatic disease or vasculitis, joint symptoms, and neurologic symptoms.

There were 17 diagnosed cases of SLE all with a positive ANA at a titer of at least 1:80. For SLE the ANA had a sensitivity of 1.0 and specificity 0.86. "Other" rheumatic diseases included drug-induced lupus, Sjogren's disease, rheumatoid arthritis, undifferentiated and mixed connective tissue disease, juvenile rheumatoid arthritis, and systemic sclerosis. When the ANA was assessed inclusive of all other rheumatic diseases, its sensitivity was 0.60 and its specificity 0.87.

The overall prevalence for rheumatic diseases within the study group was 5.6%. The positive predictive value(PPV)of a positive ANA titer≥ 1:40 was 0.11 for rheumatic diseases. The negative predictive value (NPV) of the ANA was 0.97. If a rheumatologist ordered the ANA the PPV was 0.68 significantly higher than the PPV of 0.10 in the hands of nonrheumatologists.

The receiver operator curve showed the optimum titer cutoff for diagnosing SLE was 1:80. At titers below this, the false positive rate increased. The PPV of a titer> 1:320 was 0.24 for SLE and 0.31 for other rheumatic diseases.

Comment: This retrospective study is based on a patient population cared for at a major

medical center and likely does not represent the care encountered in the average community. There was a significant difference in the positive predictive value of the ANA for rheumatic disease in the hands of rheumatologists compared to nonrheumatologists.

The higher PPV seen with rheumatologists' tests was also associated with a high prevalence of disease of 39% compared to a prevalence of 1.5% in those seen by a nonrheumatologists. Here the limitations of this retrospective study are evident as the reasons for drawing the ANA in the first place can not be taken into account.

A negative ANA appears to be efficacious in ruling out rheumatic diseases with a negative predictive value of 0.97. In considering the NPV of a negative ANA, another limitation of this study is encountered. Diagnoses were based on only several months of chart history surrounding the time of the ANA test. As rheumatic disease presents over time, one must question whether the PPV might be higher and NPV lower if a longer follow-up were available. Despite these limitations, this study shows that a positive ANA has a high PPV when a rheumatologist suspects rheumatic disease. An ANA titer greater than 1:320 represents a moderate risk of 0.31 for a rheumatic disease.

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LITERATURE REVIEW

Implantation of Pacemakers in the Elderly

John E. Kirkpatrick

Reference: Shen, W.K, Hayes D.L., Hammill S.C., Bailey, K.R., Ballard D.J., Gersch B.J. Survival and Functional Independence after Implantation of a Permanent Pacemaker in Octogenarians and Nonagenarians. Arch Internal Med. 1996; 125:476-480.

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The number of permanent pacemakers placed in the very elderly are increasing. Mayo clinic reviewed 157 patients who were 80 years of age or older treated with permanent cardiac pacing. Survival was examined and compared to expected. Although the number of patients was relatively low and over a period of twenty six years (1962-1988) there were some significant observations noted.

The two strongest independent predictors of death by multi-variable analysis were the presence of congestive heart failure an chronic obstructive pulmonary disease. Those who did not have structural heart disease had survivals similar to the expected. Interestingly, the group (18%) that received dual chamber pacing did not differ in observed survival from the group with ventricular pacing.

Patients were stratified in order to evaluate the association between survival and disease of the conduction system. Atrioventricular block and chronic atrial fibrillation with bradycardia had observed survival much worse that expected. Functional and physical independence was evaluated pre and post pacemaker placement. Fifteen percent (23/157) were in nursing homes and the time of pacing. Another 45% (70/157) were permanently placed in nursing homes after implantation. It was also noted that there was the onset of worsening of cardiac (n=20), neurologic (n=42) or orthopedic (n=41) disabilities although the severity of those changes was not apparent in the study.

Even though the numbers were small in each subset examined, this study clearly shows the relatively poor survival of many of the very elderly after cardiac pacing. The functional outcome of the survivors also indicated significant worsening disabilities. Even though the benefits of cardiac pacing are significant in a younger population, the authors clearly question the positive impact in the very elderly.

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LITERATURE REVIEW

Cardiac Troponin Levels for Risk Stratification in Acute Myocardial Ischemia

Michael L. Moore

Reference: Ohman, M.E., et al. Cardiac Troponin T Levels for Risk Stratification in Acute Myocardial Ischemia. New England J Med 1996; 335:1333-1336.

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Troponin T is the tropomyosin binding protein which is located on the contractile fibers of cardiac muscle cells. During ischemic heart injury, troponin T is released into the bloodstream. Studies previously have demonstrated a correlation between elevation of troponin T and myocardial necrosis secondary to infarction.

This study, which was a secondary investigation of the GUSTO-IIa trials, was conducted in order to determine if there was an association between troponin T levels and subsequent morbidity and mortality. The results of the study show that there is a clear correlation between elevated troponin T levels and 30 day mortality.

The results have shown that detectable levels of troponin T (0.1 ng/ml is the minimum detectable level) are associated with a 5% probability of death within thirty days. This rate rises linearly to a high of 25% thirty day mortality when associated with a troponin T level of 15 ng/mg. These findings correlated with standard methods of detection of myocardial infarction, CK-MB enzymes and EKG changes. There were several cases, however, in which the troponin T level was elevated early in the clinical presentation whereas the CK-MB and EKG changes were late findings.

From this large well conducted study, troponin T appears to be an independent factor which correlates with early mortality in ischemic heart disease. Detectable levels occur within hours of injury. The level of troponin T correlates directly with the risk for 30 day mortality with minimum detectable levels associated with 5% risk climbing to a 25% mortality at 15 ng/ml levels. While still early in the experience of troponin T, it would appear that its usage would be valuable for the insurance underwriter to help quantify the extent of damage done at the time of infarction. Clearly, the presence of a troponin T level over 0.5 ng/ml must be considered a significant risk factor for short term mortality. Studies regarding troponin T levels and long term survival have yet to be performed, but could prove to be most interesting and worthwhile.