The Perfect Storm

Cardiovascular disease (CVD) is the leading cause of death in adult men and women in the United States. CVD is also the major cause of mortality and morbidity worldwide. A dramatic increase in obesity is eroding successes in CVD risk reduction seen in recent years. Type 2 diabetes and pre-diabetes are appearing in increasing numbers in teenagers and young adults. These changes will impact the future insured populations. This constellation of impairments is changing the underwriting landscape.

The Impact of the Metabolic Syndrome

The specific components of the metabolic syndrome are outlined in Table 1. These components – upper body obesity, cardiovascular risk factors and impaired glucose function – are being studied by health care researchers and epidemiologists. Most cardiologists and internal medicine specialists believe that this is a clinically valid syndrome that impacts cardiovascular risks. For that reason, standard therapy now targets treatment for all of the components of the metabolic syndrome.

The combination of the metabolic syndrome risk factors more strongly predicts the incidence of cardiovascular disease and total mortality than its individual components (Shaista, Circulation, 2004; 110: 1245-1250). Twenty years ago, preventive cardiologists at the University of Wisconsin noted that two-thirds of patients undergoing multivessel bypass surgery had the combination of (1) hypertension over 135/85 mm, (2) HDL-C under 40 mg/dL,

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Obesity</td>
<td>Waist Circumference</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt;150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;130/&gt;85 mmHg</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>&gt;110 mg/dL</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>NCEP ATPIII. JAMA. 2001; 285:2486-2497</td>
</tr>
</tbody>
</table>

Table 1
Atherosclerosis

Lipoprotein abnormalities, hyperglycemia and hypertension are root contributors to atherosclerosis development. The prevailing belief is that atherosclerosis is an inflammatory disease. Considering the natural history of vascular disease, it is not just the severity of plaque stenosis, but plaque vulnerability and instability. Soft plaque appears to predispose diseased arteries to risk. Even mild to moderate disease can make a diseased artery vulnerable to plaque rupture in a patient, when combined with uncontrolled risk factors.

Therapeutic markers – high sensitivity C-reactive protein (hsCRP) among others – are thought to be measures of the inflammatory process leading to cardiovascular disease. hSCR is elevated in metabolic syndrome patients to a level higher than what would be expected by adding expected measurement of markers for individual risk factors (Fest et al., Circulation, 2000. 102; 4: 2-7). With rising hsCRP, the risk for developing CVD statistically increases. These factors lead to endothelial dysfunction. The endothelium is the lining layer in all arteries. The endothelium is where atherosclerosis occurs.

Coronary disease occurs when the lining of the arteries – the endothelium – is damaged. This process occurs over years and decades. Many factors known to be risk factors have been implicated in causing endothelial dysfunction and corresponding heart disease. In addition to inflammatory markers, other techniques have been developed. Dr. Robert Vogel at the University of Maryland studied endothelial dysfunction abnormalities by measuring flow-mediated vasodilatation blunting. (The arteries fail to dilate appropriately when occluded.) In the following list, modifiable risk factors are italicized:

- Increased age
- Male gender
- Family history
- High LDL
- VLDL & CM remnants
- Oxidized LDL
- Lipoprotein(a)
- Low HDL
- Smoking
- Mental stress
- Homocysteinemia
- Hypertension
- Diabetes
- High fat meals
- Obesity
- Inactivity

The impact of obesity has always been recognized, but its effect when combined with other risk factors is underappreciated, even in young children. Severely obese 12-year-olds have dramatic increases in markers of endothelial dysfunction (flow-mediated vasodilatation abnormalities) compared with those in normal children (Tounian et al., Lancet 2001; 358:1400-1404).

Underwriting Tools for Determining Cardiovascular Risks

The risks of mild or nonocclusive coronary disease may be underestimated by life underwriters. The CASS Study (Coronary Artery Surgery Study, Little WC et al., Clin.Card. 1991) identified that lesion severity may not always predict survival. Less than 17% of acute myocardial injury occurs in patients with high grade coronary artery narrowing greater than 70%. Surprisingly this study identified that the majority of myocardial infarctions occur in patients with angiographically “insignificant” disease (<50% occlusion). Unstable lesions with soft plaque can result in cardiac disease. In addition, survival in patients with high grade coronary disease varied little from that of patients with moderate coronary disease in this 7-year study.

Additionally, coronary angiography has limitations. Other technologies such as intravascular ultrasound (IVUS) may identify significant disease of the coronary artery where vessel remodeling and the presence of severe soft plaque may be present, but be missed by studies such as CT angiography.

Angiography Limitations Visualizing Coronary Remodeling

Non-Invasive Imaging Studies: CT Angiography

For many patients and applicants, there is value in evaluating noninvasive studies such as CT angiograms. Patients with high calcium scores are at a higher risk for cardiovascular events (Detrano et al., New England Journal of Medicine 2008; 258(13): 1336-1345).
As previously noted, soft plaque (noncalcified) is not identified by this diagnostic tool, and applicants who may be at risk may have low calcium scores. There are patients with unstable plaque who are at risk, especially in patients with multiple risk factors not treated aggressively.

**Obesity: Its Scope and Impact**

Approximately 122 million patients in the United States are obese or overweight. Obese men – even without other risk factors – are at increased risk for cardiovascular disease. Obesity co-exists with hypertension, hyperlipidemia and insulin resistance leading to cardiometabolic disease (Chobanian et al., *Hypertension* 2003; 42: 1206-1252).

With the rise of obesity, there has been a parallel increase in the incidence of Type 2 diabetes. In the last three decades the incidence of diabetes has nearly tripled. The south central and southeastern United States is particularly affected, reflecting demographic and regional patterns of food choices and demographics.

Abdominal obesity is present in increasing numbers in middle-aged men and women. Preventive cardiologists and epidemiologists postulate that excess upper body obesity leads to a cascade of reactions that contribute to endothelial dysfunction and the development of CVD. [see Upper Body Obesity chart, top next page.]

The effects of obesity increase with aging, and the presence of vascular disease becomes more prominent in middle age (40-65). The CV Mortality graph, [next page] is included in the Centers for Disease Control professional education series on the Metabolic Syndrome (Thomas et al., *Hypertension* 2005; 46:654-659).

**Medical and Public Health Approaches to Obesity and the Metabolic Syndrome**

*The Importance of Therapeutic Lifestyle Changes and Risk Factor Reduction*

Personal lifestyle choices and the rising incidence in obesity are leading to a significant increase in health care expenditure, and increasing disability and death. Long-term initiatives by the National Institutes of Health and the Centers for Disease Control have been introduced to stem these trends. Education of the public and health professionals is emphasizing the importance of risk factor treatment and adopting changes in lifestyle.

Several impressive studies show the powerful impact of risk factor modification. Nathan and co-workers in the Diabetes Prevention Program Group showed the effects of therapeutic lifestyle changes on the development of diabetes and related mortality. The multicenter longitudinal study, published in the *New England Journal of Medicine* in 2002 and in 2006, identified that by adopting simple lifestyle changes, the treatment group enjoyed a 12% reduction in CVD mortality and a reduction in progression to diabetes by 58%. Lifestyle changes identified in this study are:

- >7% long-term loss of body weight
- Limiting fat intake to <25% of total calorie intake (substitute fish oil, canola oil, etc.)
- Limiting calorie intake to an average of 1200-1800 kcal/day
- Walking for 150 minutes per week of physical activity

Diet
Portion size has played a major role in societal obesity. Snack food portion sizes from 1977 to 1996 dramatically increased in all categories (salty snacks, desserts, soft drinks, French fries, burgers, pizza, Mexican food) (Nielsen, SJ, Popkin, BM, JAMA 2003;289:450-453). Fried foods are traditionally a regional favorite in the southern United States, but the rest of the nation is also adopting fast foods, which frequently include fried high calorie diets. The food industry – under the threat by the FDA to label high calorie processed sugar snack foods as potentially being a health danger – are limiting sales of soft drinks in primary and secondary schools, and snack food portions will be downsized in the next few years. Unfortunately “fruit drinks” with high processed sugar content remain.

Exercise
Of all the lifestyle changes, exercise is considered to be the most beneficial, especially in diabetics, those with established CVD and patients with multiple risk factors. Recent studies confirm that exercise results in the proliferation of endothelial progenitor cells – precursors to cells important in collateral circulation. Collateral circulation is an important adaptive event that can occur in patients with occlusive atherosclerotic disease. This “self-re-vascularization” can prevent loss of myocardial tissue or peripheral vascular occlusion. The more active the patient with nonocclusive vascular disease, the more likely that the patient may postpone or in some cases prevent end organ disease (cardiac, peripheral vascular or cerebrovascular disease) (Laufs, U et al., Circulation 2004;109:220-226).

It will take years to determine if current public health initiatives to encourage medical compliance and life style changes will impact CVD mortality and morbidity. Personal habits and comfort determine behavior. UCLA preventive cardiologist Dr. George Diamond said it best: “Will power lasts about two weeks – and is soluble in alcohol!” Dr. Diamond’s statement regarding human behavior (and not intoxicants) does point out that the challenge is significant given societal eating habits.

Treatment of Hypertension
Lewington et al. published a meta-analysis of 61 combined prospective or observational studies involving 1 million adults. The study demonstrated that even a modest reduction of systolic blood pressure average of only 2 mmHg in this population could reduce mortality from ischemic heart disease by 7% and from stroke by 10% (Lewington, S et al., Lancet 2002; 360:1903-1913).

The benchmark Framingham Study identified that “high normal” hypertension (blood pressure of 130-139 mm systolic/85-89 mm diastolic) is not benign. Compared with women with a normal blood pressure (120-129 mm systolic and 80-84 mm diastolic) the
cumulative incidence of cardiovascular events is 2.5 times greater (in men, the risks are 1.8 times greater). (Vasan, RB et al., NEJM 2001;345:1291-1297).

A recent article by Copley et al., reported the combined results of 10 respected clinical studies (>100,000 patients) including studies by the VA hospitals, United Kingdom diabetic study and at-risk patients, including African-Americans and patients with established renal disease (Copley, Dis Mon 2005: 51:548-614). The cumulative results demonstrate that blood pressure is frequently undertreated by most practitioners. Most patients require two or more medications to reach a systolic blood pressure between 130-144 mm systolic. Combination therapy is now common.

The American College of Cardiology Foundation and the American Heart Association have just issued new guidelines in 2011 for patients over the age of 65. In general, blood pressure should be targeted as 140/90 or lower. In patients over 80, the goal for systolic blood pressure is 140-145 mm Hg. Hypertension is identified in 75% of patients who are obese. Less than 10% of patients who are normal weight have hypertension.

**Current Benchmark for Treating Diabetes and Pre-diabetes**
The treatment of metabolic syndrome and pre-diabetes has changed dramatically in the last decade. Primary care physicians and nurse educators are highlighting the need for aggressive therapy in both the metabolic syndrome patient and in the early diabetic. Early treatment results in a significant reduction in risks of medical complications or mortality. The UKPDS (United Kingdom Prospective Diabetic Study) confirms several important findings:

1. To lower mortality, tight blood pressure control is more effective than tight glucose control.
2. Tight glucose control may have a paradoxical effect on mortality (hypoglycemia and its complications).
3. In patients who progress from pre-diabetes to diabetes, aim to get hemoglobin A1c levels around 6.5%.
4. Weight reduction reduces the risk of diabetes. Combination oral therapy is now available in diabetics. Compliance increases with combination pills, but so does cost. Supplemental insulin is becoming much more common in the treatment of uncontrolled Type 2 diabetes. Aggressive treatment in both the pre-diabetic and the diabetic patient is evidenced by physicians treating patients with aspirin, ACE-1 inhibitors, angiotensin receptor blockers (ARBs) and lipid control. Weight loss combined with calorie control and increased exercise is most effective.

**Cholesterol Management**
The treatment of lipid abnormalities has also become more focused and treatment is more aggressive. Patients with identified coronary artery disease, prior myocardial infarctions, prior cerebrovascular accidents, peripheral vascular disease, diabetics, smokers and patients with metabolic syndrome should be treated to LDL-C levels <100 mg/dL (and many preventive cardiologists target LDL-C goals at <70 mg/dL) (Grundy, SM et al., Circulation 2004;110:227-239 and Smith, SC Jr et al., Circulation 2006; 113:2363-2372).

In the NEPTUNE Study, Davidson et al. studied very high risk patients with cardiovascular disease, metabolic syndrome patients, diabetics and smokers. Doctors were able to attain an LDL-C of <100 mg/dL in 54-60% of patients. In those at the highest risk, doctors were able to reach an LDL-C <70 mg/dL in only 18-22% of patients. Unfortunately, many high-risk patients did not reach LDL goals, despite treatment plans.

The National Cholesterol Education Panel and the American College of Cardiology remind us that patients with low protective HDL cholesterol, especially with other risk factors, should be considered for aggressive medical treatment of LDL. Low HDL cholesterol is one of the hallmarks of metabolic syndrome, and aggressive LDL-C therapy goals should be considered (i.e., <70 mg/dL optimal, <70 mg/dL goal). It is also common to see elevated triglyceride levels in this treatment group, and an increased risk of insulin resistance and eventual development of diabetes. NCEP and ACC goals for at-risk patients are as follows:

- LDL-C <100 mg/dL—optimal (<70 mg/dL in high-risk patients)
- HDL-C <40 mg/dL (<50 in women is recommended in metabolic syndrome)
- Lower triglyceride classification cut points
  - More attention to moderate elevations >200 mg%
  - Lower non-HDL cholesterol (T-Chol - HDL-C)

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<table>
<thead>
<tr>
<th>For every decrease of Hgb A1c by 1% can reduce:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths from diabetes</td>
</tr>
<tr>
<td>Heart attacks</td>
</tr>
<tr>
<td>Microvascular complications</td>
</tr>
<tr>
<td>Peripheral vascular complications</td>
</tr>
</tbody>
</table>
Since benefits for preventing heart disease is well established, cholesterol-lowering statins continue to be first-line treatments for heart patients. However, there is less evidence that statins reduce the risks or prevent problems in those who have no history of CVD.

**Will Incentives or Disincentives Aid in Reducing CVD?**

Health care providers in managed care and patients are being offered incentives to reach treatment goals. Targeted are patients with metabolic disease or diabetes. Some health plans are offering significant discounts for participations in health clubs or documented compliance with treatments and weight loss.

**A Hope for Gene Therapy in Preventing and Treating Cardiovascular Disease**

Genetic research and the Genome Project are leading to increased understanding of the impact of obesity and the metabolic syndrome. Genetic research has identified the FTO gene in Type 2 diabetics. The gene is also present in nondiabetics and is associated with increased BMI. Sixteen percent of Caucasian adults and children carry two copies of this variant, and 41 collaborators found that the rate of obesity and increased BMI was 67% higher than matched patients without the FTO gene. Additionally, Lifton and co-workers identified causative mutation in isoleucine transfer RNA. This discovery recognizes that this mitochondrial mutation leads to the metabolic syndrome constellation (Hattersley, A, McCarthy, M, *Science* 2007; 316:185). It is likely that mitochondrial dysfunction occurs with aging, and in the metabolic syndrome, is associated with dietary excess and inactivity. Such studies may lead to therapeutic advances in treatments for those at-risk patients (Wilson, Lifton R et al., *Science* 12 Nov 2004; 1190-1194. Barch, GS et al., *Nature* 2002-2004; 404: 644).

**Underwriting Implications**

Underwriting can be challenging when the risk factors in metabolic syndrome independently indicate only minor, if any, mortality concern. Yet, the collective risk cannot be ignored. Combining the upper body obesity with hypertension, lipid abnormalities and impaired fasting glucose is the approach an underwriter must take to proper risk classification. In addition, the applicant’s cardio-respiratory fitness and medical therapy compliance should be considered when determining underwriting offers.

Medical histories available in attending physician statements or by questionnaires are valuable sources of information. In addition to getting medical history that includes height and weight, information such as waist size or body surface area (BSA) measurements can be helpful.

Underwriters and actuaries rely on extensive scientific data and statistical trends when determining mortality risk. Underwriters rely on diagnostic studies such as coronary angiography and other imaging studies that provide guidance in classifying risks. Underwriters know the limitations of these studies and are able to incorporate that into the risk assessment process.

However, the impact of patient behaviors, including medication compliance and persistence in staying active and following dietary recommendations, can have a significant effect on mortality and morbidity results. Yet, they are not easy to measure. Nevertheless, focusing on patient behaviors and new testing protocols can add a new and positive dimension to the risk classification decision.

Critical to the underwriting assessment is an evaluation of the medical treatment of established cardiac risk factors. Attention must be paid to the number of antihypertensive agents and the success of therapy. Good blood pressure control is essential. Likewise, underwriters should look for the effectiveness of therapy in hyperlipidemia histories.

**Summary**

- The appropriate underwriting approach considers the combination of obesity (particularly upper body obesity) with hypertension, lipid abnormalities and impaired fasting glucose.
- Effective cardiometabolic risk factor reduction improves underwriting risks.
- Documentation of treatment and therapeutic lifestyle change compliance support a more positive underwriting position when evaluating risks.
- While advances in therapy have decreased cardiovascular risks, societal behavioral changes need to be implemented to reduce population risks.
- The application of genetic discoveries may affect risk classification decisions.

**Bibliography**


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