Guidelines Recommendations

Worldwide obesity accounts for approximately 58%, 21%, 8-42% and more than 10% of diabetes cases, ischemic heart disease, certain cancers and deaths respectively. (World Health Report 2002 Geneva, World Health Organization) The Framingham study shows that obesity hazards risk for heart failure is 1.46, 1.23 -1.7 (females) and 1.37, 1.13 -1.67 (males) in 20 years. (Kenchaiah, NEJM ’02;347:305) Consensus is meager regarding the ideal approach to weight reduction due to disappointing lifestyle changes to encourage weight reduction that were attempted by 25% and 43% American men and women respectively. Pharmacotherapy and bariatric surgery long-term success, risks and cost-effectiveness have also not been fully evaluated. (Manson, Arch Intern Med 2004; 164:249) Without precise estimates of the benefit and with substantial variability in intervention strategies, it is currently impossible to estimate the cost-benefit ratio of weight loss programs. However, the National Heart, Lung, and Blood Institute and the North American Association for the Study of Obesity proposed weight loss strategy to include calorie restriction, structured physical activity, behavioral therapy and psychological support for patients with a BMI > 30 kg/m² and those with a BMI of 25.0 to 29.9 kg/m² with a history of CHD or two or more atherosclerotic disease risk factors. (Washington, DC, National Heart, Lung, and Blood Institute, 2000)

Even if the program recommendations are evidence-based, currently there are valid concerns. Unfortunately, clinical practice guidelines may have to depend on less high-powered evidences. For example, in well studied STEMI trials, only 13% of the ACC/AHA guidelines recommendations are based on ‘level A’ evidence, i.e. from multiple large randomized clinical trials. (Tricoci, JAMA ’09;301:831) Furthermore, strength of evidence is often heavily based on statistical significance results, that maybe trivial compared to null, with less attention on clinical and practical importance of the treatment effects. (Kaul, J Am Coll Cardiol 2010;55:415). ‘Comparative effectiveness research’, based on large RCTs to reduce biases, is dependent on which patient-subgroup will benefit the most from certain treatments to guide personalized care. (Gitt, Eur Heart J ’10;31:525) Even a well-conducted and internally valid trial that include a highly selected population under controlled conditions may not be readily extrapolated to individual cases. (Granger, Eur Heart J ’10;31:520) This presentation intends to present caveats and idiosyncrasies to “blind- student-followers” to guideline recommendations since RCT’s outcomes do not necessarily translate into individualized benefits. Without a “hook-line-sinker” attitude to “evidenced-based” data an individualized practical risk reduction strategy is suggested.

Recommendation Success Measures

In any intervention or treatment strategy, success or otherwise require measurable outcome that should be practical, inexpensive, reproducible, patient friendly with motivation for long-term adherence. Furthermore, consider also that any risk factor that can trigger a patho-physiologic mechanism do not necessarily kill unless target organ damage (TOD) has occurred. However, with or without co-morbidities of components comprising the “metabolic syndrome”, obesity, for example, can be an independent heart failure hospitalization risk due to adipose cells related lipid toxicity cardiomyopathy. (Yudkin JS, Lancet 2005; 365: 1811-820) Moreover, obesity problem is often related to pre-existing clinical conditions. Or obesity maybe a compounding risk to hypertension or diabetes. Or obesity may compromise heart failure, renal insufficiency or COPD treatment strategies. In such situations, target outcome is secondary prevention of major adverse cardiovascular events (MACE) or mortality. On the other hand, primary prevention of any disability or quality of life impairment may be a target endpoint. Whether primary or secondary preventive action plans, time maybe a major deterrent to objectively assessing management benefits. Most randomized trials often take at least 2-3 years to attain statistically significant outcomes. What then are a provider and receiver customized and manageable strategy?

Definition Gold Standard

First, temporal definition of obesity, can influence any method of establishing any epidemiological or outcome data. BMI is the obesity index in children and in adolescence. Furthermore, waist-hip ratio or waist circumference is more applicable to adults. Retrospective annual weight recorded data can reflect trending changes. But, case finding of weight levels frequently accompany consultations that may not necessarily be related to the obesity issue. Prospective studies can have weight issues as a variable risk. Obesity may also appear to be a geographical variation. It is also of interest that the age-adjusted decline in weight may not
change event rates that are sudden and unexpected as in non-witnessed sudden death. Furthermore, the decreasing age-adjusted obesity rates do not imply a decrease in absolute numbers of events because growth and aging in any population may increase obesity prevalence. Thus, prevalence changes have definition idiosyncrasies and with compounding variable influences such as sex, age groups among others.

Three factors are of prime importance for identifying populations at risk and consideration of strategies for prevention or control of obesity. (1) the clinical subgroups in which obesity occurs (prevalence); (2) the absolute numbers and event rates (incidence) among population subgroups; and (3) the time dependence of risk (trending in observational studies or registry data.)

**Prevalence Issues**

How achievable is prevalence changes as an endpoint? Obesity prevalence based on 2008 NHANES data do provide local background data. It may take several years, however, to change population screened obesity prevalence that may not even involve obese cases subjected to intervention projects. More importantly, as pointed out in a Texas Heart Institute Journal Editorial, data should “distinguish between population medicine and individual medicine.” Moreover, trial duration has to be factored in. (Michel Accad and Herbert L. Fred, Texas Heart Inst. J 2010;37:6) Furthermore, existing reviews pool data on outcomes, many do not identify the sex of the population suggesting incomplete reporting in the trials. But treatment and outcomes do vary by sex. (Clark, J Am Coll Cardiol 2009;54:397). Thus, prevalence data changes is time dependent and randomized studies outcome do not necessarily reflect on individual cases particularly in the absence of sex identity.

**Incidence Estimates**

Estimates of incidence (percent/year) may include the total number of events per year for the general adult population that should also reflect on high-risk subgroups. Due to increasingly co-morbid risk factors, obesity incidence may increase progressively, but maybe with a progressive decrease in the total number of events represented by each group. “The inverse relationship between incidence and total number of events occurs because of the progressively smaller denominator pool in the highest subgroup categories. Successful interventions in larger population subgroups require identification of specific markers to increase the ability to identify specific patients who are at particularly high risk for a future event. The natural history of a population of patients with major risk factors or known cardiovascular disease but at low risk because of freedom from major cardiovascular (CV) events is compared with patients who have survived a major CV event. Attrition over time is accelerated for the initial 6 to 18 months after the major CV event. After the initial attrition, the slopes of

the curves for the high-risk and low-risk populations diverge less, highlighting both the early attrition and attenuation of risk after 18 to 24 months”. These relationships have been observed in diverse high-risk subgroups (e.g., cardiac arrest survivors, post–myocardial infarction patients with high-risk markers, recent onset of heart failure). (Myerburg, Circ '92; 85(Suppl I):12 & J Cardiovasc Electrophysiol '01;12:369) Thus, mean events incidences may be over or underestimated depending on event rates among high risk subgroups with pre-existing CV events in the study population.

**Observational Pitfalls**

There are potential pitfalls in observational analyses even for weight reduction strategies. For example, fibrinolysis in the elderly based on a financial claims database analysis otherwise. (Gitt. Eur Heart J '10;31:525). Likewise, hormone replacement therapy and vitamin E, appear to be beneficial in carefully conducted observational studies, only to be found to be neutral or harmful in definitive randomized trials. (Granger, J Am Coll Cardiol '06;48:434) A recent careful analysis from Vancouver showed that statin adherence was strongly and independently associated with lower risk of motor vehicle accidents, accidents in the workplace, greater use of screening strategies, and lower mortality from other diseases. However, there are no biological or mechanistic explanations for these benefits from statin therapy (Dormuth, Circ '09;119:2051) Moreover, observational HF mortality in different European countries is 13% to 30%. In a cross-sectional epidemiological study in Rotterdam, the average age of HF was 77 years that is more than 10 years and the 2-years survival was 59%-79% at 5 years, about twice less than that of age-match peers. (Cowie, Eur Heart J ’01;22:1247) Thus, observational morbid and mortality statistics may likely differ significantly from the real world scenario, at best hypothesis generating and can’t be the basis for individual program.

**Registry Data Assests**

A major advantage of a registry is the inclusion of the entire spectrum of the patient population with a particular disease or syndrome, inclusive of patients with many co-morbidities that maybe under-represented in most clinical trials but can also include dosing risk-prone cases. (Alexander, JAMA '05;294 3108) Furthermore, the follow-up in prospective registries: 1) is considerably longer than that of most clinical trials; 2) can assess and compare different current clinical practice guidelines and outcomes;3) can contribute to quality assurance, indicating areas where education is necessary; 4) can increase adherence to guidelines; 5) can determine areas with suboptimal or conflicting practices with guideline recommendation among geographical areas or patient sub-groups; and 6) can show that adequate adherence to guidelines can influence survival rates. (Gitt. Eur Heart J ’10;31:525) However, in a
polypill situation and without serum drug levels, specific drug advantage can be merely implied. But combination of high quality clinical trials and prospective registries can best define and apply effective therapies and can provide answers to different questions. Thus, complementary RCT and registry directed therapies may approach real world scenario particularly if guidelines’ recommendations depend on less than 15% large RCTs. What then is the most practical, least expensive and easily duplicated strategy that may provide short and long-term outcome measures that can be relevant not only to the researchers but also to the concerned individual subjects?

Current Anti-Obesity Methods

Obviously, dietary advisories and exercise that are intended to reduce input and increase output of calories respectively are advocated. Yet, do dietary or caloric intake advisories matter most? It is NOT THE FOOD but HOW YOU EAT that matters, DISCIPLINE AND COMPLIANCE is more important than DIET COMPOSITION. Although low CHO diet may give a better short-term weight reduction effect, low-fat diet may have a longer weight reducing effect. (Shia, NEJM ;08;359:229) Or, weight changes maybe similar regardless of diet type but HDL-C is higher with low-CHO diet. (Davis, Diab Care ’09;32:1147) What matters is the caloric count loss. It is also NOT THE TYPE OF PHYSICAL ACTIVITY but HOW MUCH EFFORT IS EXERTED that matters. For example, those involved in the “dignity of labor” jobs may utilize a cumulative daily energy loss equivalent to that used during a 45-minute structured exercise work-up. ADHERENCE being a major issue, simply monitoring weight changes may not be enough incentive to reduce weight. (Apple, JAMA ’05;294:2455) Problematically, tracking obesity prevalence, even utilizing random sampling, may take years to show any meaningful interventional results. What then is another option?

Six-minutes Walk

What is needed is an objective performance measure that can readily impart a sense of success, non-improvement or failure of any intended action plan within an acceptable time frame. The distance covered within a six-minute-level-walk test is an objective assessment of functional capacity. After-all, attaining preferred weight must translate into improved or desirable pchrono-tronic competence. The predicted maximum HR (PMHR) at end of a 6-minute walk can reflect on sympathetic tone. Peak HR \( (220 - \text{age}) = \% \text{PMHR} \), as achieved sympathetic activity competency. Vagal tone is reflected by the HR recovery index (HRRi) that is obtained by \((\text{Peak walk HR bpm}) - (1 \text{or 2-minutes rest HR bpm})\). (Two-minute HRi bpm) \((25 \text{bpm as threshold of vagal tone dysfunction}) = \% \text{HRRi} \) indicating vagal tone competency. Thus, the six-minute walk can reflect objectively maximal or sub-maximal functional capacity as well as on-target or below-target autonomic tone changes. (Lauer, JACC ’98;32:280, Keys, Texas H Inst J’09;36:282; Gibbons, Lancet’02;359:1536) The 6-minutes test is an individualized performance measure independent of mean population or group performance data base. More importantly, autonomic dysfunction and impaired treadmill testing functional capacities have prognostic implications. Mortality risk for treadmill ECG ischemic ST changes is 12%; chronotropic incompetence- 15%; attenuated HRRi- 17%; impaired functional capacity- 23%; and poor HRRi + poor functional capacity- 45%. (Messinger-Rapport, J Am Geriart Soc ’03;51:63)

Summary

Trending changes based on prevalence, incidence or registries are population or group data with compounding variables, risk and time dependent biases and may not truly reflect affectivity of proposed weight reductions strategies. Even randomized controlled studies’ outcomes maybe flawed and may not necessarily extrapolated to specific individual who may explicitly different from the trial profiles. A personalized motivating method to evaluate personalized weight changes is the level 6-minute walk test inclusive of chronotropic competence analyses.