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Does Modern Medicine Increase Life-expectancy: Quest for the Moon Rabbit?

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"What is the goal of medical treatment:
Is it alleviating discomfort or lengthening lives?"

ABSTRACT

The search for elixir of immortality has yielded mixed results. While some of the interventions like PCI and CABG have been a huge disappointment at least as far as prolongation of life is concerned: their absolute benefit is meager and that too in very sick patients. Cardiac specific drugs like statins and aspirin have fared slightly better, being useful in patients with manifest CAD, particularly in sicker populations although even their usefulness in primary prevention is rather low. The only strategies of proven benefit in primary/primordial prevention are pursuing a healthy life-style and its modification when appropriate: like cessation of smoking, weight reduction, increasing physical activity, eating a healthy diet and bringing blood pressure, serum cholesterol and blood glucose under control.

INTRODUCTION

Mortality has tormented human consciousness since time immemorial and humankind has perpetually searched for a therapy that extends life, the so called Philosopher's Stone. In this quest the human race has been only partially successful; the life expectancy has certainly increased but only upto a certain point. "Nobody has yet achieved even modest life extension beyond the apparent upper limit of about 120 years." Thus along this road there have been some successes but mostly disappointments. Typically, when a "new therapy" is introduced there is a lot of hope but as its use increases, its side-effects also become apparent, which starts a whole new drive towards next generation of this therapy which is safer and more effective, but then even newer side-effects come up again and this cycle goes on and on; something like "Carrot and the Horse." Further, the effects of a new therapy are more remarkable when disease has already occurred (secondary prevention) and already reduced life expectancy as a result of this disease; the more severe / serious the disease, the greater possible benefit of the therapy. However, although effective therapy may reduce the mortality arising of this disease but practically never brings it back to normal, "the Zenos's Paradox." Recently, advanced technology has provided us with two highest-profile treatments for coronary artery disease (CAD): coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI). Each intervention in itself promised a lifesaving relief and consequently was embraced enthusiastically by physicians and even lay public. Both these techniques indeed often provide rapid, dramatic reduction of the alarming pain associated with angina. Yet, when it comes to prolonging life, their track-record is near dismal providing little or no improvement in survival rates over standard medical and lifestyle therapies except in the sickest of the patients. Further, these procedures are also associated with significant side-effects. "Doctors generate better knowledge of efficacy than of risk, and this skews decision making," says David Jones Ackerman professor of the culture of medicine.[1] But why blame only physicians, even "patients are wildly enthusiastic about these treatments," he says. "There've been focus groups with prospective patients who have stunningly exaggerated expectations of efficacy. Some believed that angioplasty would extend their life expectancy by 10 years! Angioplasty can save the lives of heart-attack patients. But for patients with stable coronary disease, who comprise a large share of angioplasty patients? It has not been shown to extend life expectancy by a day, let alone 10 years—and it's done a million times a year in this country."

So are any interventions at all which can increase the expectancy of life particularly in context of cardio-vascular conditions?

HISTORY OF INCREASE IN LIFE-EXPECTANCY

Worldwide life-expectancy at birth was 30.9 years in 1900, 46.7 in 1940, 61.13 in 1980.[2] As seen there was a dramatic improvement in life-expectancy after 1940 which could be attributed to three factors:

1. A wave of global drug and chemical innovations; penicillin, streptomycin, vaccines, discovery of DDT etc.
2. Spread and availability of medical and public health technology to all, including poorer countries.
3. Change in international status (value) of health which practically became a "right," upgraded from mere "desirable."

While early improvement in life-expectancy was a result in control of infectious diseases, subsequent improvement occurred as a consequence of focus on life-style diseases. From 1991 to 2004 life-expectancy in US improved by 2.33 years mostly by medical innovation (discovery and

availability of new drugs) but also addressing problems like smoking and obesity. [3] In context of CVS diseases mortality from heart disease in the US fell by more than half between 1950 and 1995, with a resultant increase in life expectancy of approximately 3½ years, half to two-thirds of which has been attributed to coronary care units, treatment of hypertension, and medical and surgical treatment of coronary artery disease. [4, 5]

APPROACHES TO IMPROVING LIFE EXPECTANCY

Improvement of life-expectancy with any maneuver essentially depends on;

Severity of disease – Baseline mortality is the most important factor operative on lifespan-gain from any procedure. Diseases with a higher baseline annual mortality rate demonstrated more lifespan gained. Thus therapeutic maneuvers provide more survival benefit in secondary prevention than primary or primordial prevention.

Duration for which intervention is applied – age of the patient

PRIMORDIAL PREVENTION – HEALTHY INDIVIDUAL

Caloric restriction

Caloric restriction is the only consistently reproducible experimental means of extending mean and maximum lifespan. Laboratory experiments show markedly decreased morbidity in laboratory mammals that are fed to only 80% full.[6] Indirect human proof comes from Okinawa, a region in Japan which boasts one of the longest life expectancies for its population in the world as also having a significantly large population of centenarians (living within the region) despite being one of the poorest regions in the country (being the bottom ranked in socioeconomic indicators for Japan). This is attributed to diet, high levels of physical activity, and strong cultural values that include good stress-coping abilities. Among the peculiarities of culture Okinawa culture embraces Hara Hachi Bu, which means to eat only until 80% full. [7] Further, studies on the oldest living natural population in the world, the Seventh Day Adventists living in California, support these findings. [8] Long-term human trials of CR are now being done. More recent work reveals that the effects long attributed to caloric restriction may be obtained by restriction of protein alone, and specifically of just the sulfur-containing amino acids cysteine and methionine.[9,10]

Increased Physical Activity

Undertaking regular exercise (jogging) increases the life expectancy of men by 6.2 years and women by 5.6 years, as per data from the Copenhagen City Heart study presented at the EuroPRevent2012 meeting. It showed that between one and two-and-a-half hours of jogging per week at a "slow or average" pace delivered optimal benefits for longevity. [11]

Metformin

A study by Bannister and co-workers revealed that patients with type 2 diabetes mellitus (DM) initiated with metformin monotherapy not only had 38% better survival than those with DM and treated with sulphonylurea (0.62, 0.58–0.66), but unexpectedly survived 15% longer than even matched, non-diabetic controls (0.85, 95% CI 0.81–0.90).This brings out an interesting prospect of metformin as first-line therapy and may imply that metformin may confer benefit in non-DM.[12]

Geroprotectors

Experimental proof of this class of drugs comes from rapamycin. It is an immune-modulator (also the drug in drug-eluting stent) which was found to lengthen the mices' lives by up to 14 per cent. Likewise, everolimus was found to partially reverse the immune deterioration that normally occurs with age in a pilot trial in people over 65 years old. The drug acting by inhibiting a protein called mTOR (interestingly mTOR also seems to be affected by calorie restriction) improved participants' immune response and is involved in sensing the level of nutrients available within cells, shifting cells into energy-conserving mode, which has anti-ageing effects, including that on the immune system.[13]

In addition to rapamycin analogs, resveratrol, found in grapes, and pterostilbene, a bio-available substance, found in blueberries have also shown favorable response.[14] Scientists estimate that these drugs could increase life-expectancy by 10 years.

Senolytics

Investigators from The Scripps Research Institute, Mayo Clinic and other institutions have identified a new class of drugs that in animal models dramatically slows the aging process, alleviating symptoms of frailty, improving cardiac function, and extending a healthy lifespan. The 2 drugs are dasatimib (an anti-cancer drug) and quercetin (a natural compound found in many fruits, vegetables, leaves and grains), an antihistamine and anti-inflammatory — can kill senescent cells. Senescent cells have stopped dividing and accumulate with age, are a non-productive burden on the total cell population, accelerating the aging process.[15]

Genome Sequencing

Geneticist Craig Venter announced he is pursuing a goal of extending and enhancing the healthy and high performance life-span by employing the power of human genomics, informatics, next-generation DNA sequencing technologies and stem cell advances.

Maintaining Ideal Cardiovascular Health

In the middle ages of human life-history, the major diseases limiting the life-expectancy are cerebro-vascular diseases and cancer. Thus it is not surprising that attempts to prevent the occurrence of CVS diseases (primordial prevention) would have an impact on increasing life-expectancy. The best way to do that seems to be to remain at a level of health which does not permit risk factors to appear (As defined by American Heart Association [AHA]). It has been suggested that community-based primordial prevention is capable of reducing cardiac deaths by 90% and prolonging life-expectancy by 10

Table 1: Reduction of Life-expectancy with risk factor

Risk Factor	Reduction in Life-Expectancy (years)
Smoking	13.9
Obesity	4
Physically inactive in leisure time	3.6
High Blood Pressiure	2.4
Vegetable / Fruit intake <5 / day	1.3

years.[16,17] It involves following health behavioral lifestyle characteristics:[18]

1. Not smoking or quitting over 1 year ago.
2. A body mass index≤ 25 kg/m2.
3. Exercising at a moderate intensity ≥150 minutes (or 75 minutes at vigorous intensity) each week.
4. Eating a "healthy diet": adhering to four to five important dietary components - sodium intake, 1.5 g/day; - sugar-sweetened beverage intake,36 oz weekly; - 4.5 cups of fruits and vegetables/day; - three 1 oz servings of fiber-rich whole grains/day; - two 3.5 oz servings of oily fish/week.
5. Maintaining total cholesterol ≤200 mg/dL.
6. Keeping blood pressure≤ 120/80 mmHg.
7. Maintaining fasting blood glucose ≤100 mg/dL.

PRIMARY PREVENTION OF CAD

Risk Factor Modifications

Mere presence of risk factors leads to reduction in life-expectancy (Table 1). Thus, logically correction of risk factors will be expected to lead to at least partial restoration of life-expectancy (Table 2). Measures used in primary prevention customarily include smoking cessation, diet modification, physical activity, weight management and correction of high blood pressure. Since the reduction of life-span is maximum with smoking, smoking cessation is likely to benefit most and it has been estimated that the risk attributable to smoking returns to baseline (nearly 14 year gain in life-expectancy) after 5 year of smoking cessation.[19] Likewise a 10mm drop in systolic blood pressure may reduce cardiovascular mortality by upto 40%.[20]

Another study noted that on average, male smokers would gain 2.3 years from quitting smoking; males with hypertension would gain 1.1-5.3 years from reducing their diastolic blood pressure to 88 mm Hg; men with serum cholesterol levels exceeding 200 mg/dl would gain 0.5-4.2 years from lowering their serum cholesterol level to 200 mg/dl; and overweight men would gain an average of 0.7-1.7 years from achieving ideal body weight. Corresponding projected gains for at-risk women are 2.8 years from quitting smoking, 0.9-5.7 years from lowering blood pressure, 0.4-6.3 years from decreasing

Table 2: Improvement in Life-expectancy with control of risk factor

Risk Factor Reduction	Improvement in Life-Expectancy (years)
Male	
Smoking Cessation	2.3
DBP reduction ≤ 88 mm Hg	1.1-5.3
Total Cholesterol ≤ 200 mg/dl	0.5-4.2
Reduction of Weight	0.7-1.7
Female	
Smoking Cessation	2.8
DBP reduction ≤ 88 mm Hg	0.9-5.7
Total Cholesterol ≤ 200 mg/dl	0.4-6.3
Reduction of Weight	0.5-1.1

serum cholesterol, and 0.5-1.1 years from losing weight.[21] Eliminating coronary heart disease mortality is estimated to extend the average life expectancy of a 35-year-old man by 3.1 years and a 35-year-old woman by 3.3 years.[22]

Statins

Statins have been hailed by many as "wonder drugs", with some physicians suggesting mass treatment of population. Dr John Reckless, chairman of Heart UK and a consultant endocrinologist at Bath University went as far as suggesting they should be added to the water supply. Some advocate it being put in table salt like "Iodine." The question is whether statins are really the wonder drugs they've been made out to be? Particularly in context of primary prevention (what to talk of primordial prevention) their role is controversial. While early trials predicted a modest reduction in mortality and a meta-analysis (14 randomised control trials{RCT}; 34,272 participants) demonstrated an all-cause mortality reduction of 16% (RR 0.84, 95% CI 0.73 to 0.96), the analysis was criticized because many of the trials included diabetics and patients with micro-albuminuria (now considered CAD equivalents) and so these trials were not purely of primary prevention. [21] On the other hand another meta-analysis of 11 RCTs involving 65 229 individuals completely free from CVD at baseline demonstrated that use of statins in this high-risk primary prevention setting was not associated with a statistically significant reduction (risk ratio, 0.91; 95% confidence interval, 0.83-1.01) in the risk of all-cause mortality.[23] Likewise an NNT review for Statin Drugs Given for 5 Years for Heart Disease Prevention (Without Known Heart Disease) revealed that no life was saved consequent to their use.[24]

Aspirin

The role of aspirin (ASA) in primary prevention of CAD is also controversial. While use of ASA is definitely of use in prevention of CAD, the balance between vascular

Table 3: Risk-benefit analysis of ASA in primary prevention

Primary Prevention	Benefit (Number of patients in whom a major vascular event is avoided per 1000/year)	Harm (Number of patients in whom a major GI bleeding event is caused per 1000/year)
Men at low-to-high cardiovascular risk	1–3	1–2
Essential hypertension[1]	2	1–2

events avoided and major bleeds caused by aspirin is substantially uncertain. A recent meta-analysis shows that for individuals without pre-existing vascular disease, the reduction of cardiovascular events after adding long-term aspirin are likely to be of similar magnitude as the hazards Table 3.[25,26]

STABLE CAD

Statins

There's little doubt that statins are effective in reducing mortality and heart attacks in patients with manifest CAD. Several large controlled trials including 4S, CARE, LIPID, HPS, TNT, MIRACL, PROV-IT and A to Z have shown relative risk reductions between 7% on the low end (in MIRACL) and 32% on the high end (in 4S), with an average relative risk reduction of about 20%. However, the sobering aspect is that absolute risk reductions are much more modest. They range from 0.8% in MIRACL on the low end to 9% in 4S on the high end, with an average of 3%. A meta-analysis of data from 90 056 participants in 14 randomized trials of statins found that across all the RCTs, statin treatment was associated with a statistically significant 12% reduction in all-cause mortality (RR 0.88, 95% CI: 0.84, 0.91, p<0.0001). On the flip-side, majority of patients saw no benefit at all and only 1 in 83 had their lifespan extended (was saved from a fatal heart attack).[27,28]

Aspirin

The classic Antiplatelet Trialists' Collaboration (an analysis of RCTs of anti-platelet therapy among more than 54 000 high-risk patients with prior evidence of cardiovascular disease) revealed that aspirin therapy reduced by about ¼ the risk of composite of nonfatal MI, nonfatal stroke, and vascular death (vascular event). Practically, this benefit translated to reduction of 1 vascular event out of 50 patients treated for 1 year.[29]

Renin Angiotensin System

Nishino and co-workers investigated the effect of angiotensin-converting enzyme inhibitors (ACE-I) / angiotensin receptor blockers (ARB) on survival benefits in patients with stable CAD (CAD but without MI). They found that all-cause (5.2% vs. 5.6%, P=0.56) and cardiovascular (3.2% vs. 3.0%, P=0.23) mortality were similar regardless of whether ACEI/ARB were used or not.[30] On the other hand HOPE study showed that ACEI therapy may reduce SCD mortality in those with CAD, stroke, peripheral vascular disease, or diabetes and at least one other cardiovascular risk factor. Over a mean follow-up period of five years, the relative risk of SCD was reduced by approximately 40%, although the absolute risk was low in both treatment and control groups (0.8 vs. 1.3%, respectively).[31]

Beta Blockers

A post-hoc analysis of CHARISMA trial revealed that in known CAD but without MI, β-blocker use was not associated with lower ischemic outcomes, but rather a trend toward a higher stroke risk (3.5% versus 1.5%; hazards ratio, 2.13; 95% confidence interval, 0.92–4.92; P=0.079).[32]

Coronary Artery Bypass Grafting

First successful CABG procedure was performed by Rene Favaloro of the Cleveland Clinic in 1968. Favaloro's report fired the imagination of many surgeons, initially operating on stable patients but as skill was acquired on ever-sicker patients, and even during MI. By 1977 cardiac surgeons were performing 100,000 bypass procedures per year based only on case reports with no single trial available to justify its usefulness. "Surgeons said trials were totally unnecessary, as the logic of the procedure was self-evident, you have a plugged vessel, you bypass the plug, you fix the problem, end of story." But there was a 'a fly in the ointment,' The first RCT of CABG, from Veterans Administration hospitals, published in 1977 revealed that there was no survival benefit in most patients who had undergone CABG versus those receiving standard medication. During this time there were two other separate multicenter, RCTs: the European Coronary Surgery Study and the Coronary Artery Surgery Study which showed however, that in some high risk sub-set of patients of CAD; significant obstruction of the left main coronary artery, triple-vessel CAD and left ventricular (LV) systolic dysfunction, and two-vessel CAD plus proximal left anterior descending coronary artery disease there could be a benefit.[33-35] However, even this survival advantage vanished on longer term follow up (12 years or more).[36] On the other hand a recent network analysis evaluating 95 trials and 93 553 [patients did reveal that CABG reduced an all cause mortality by 20% (rate ratio 0.80, 95% credibility interval 0.70 to 0.91). Thus the current evidence shows that CABG may improve survival for a few patients with the most severe forms of CAD, but for most others while it relieves symptoms but may not improve life-expectancy.

Percutaneous Coronary Angioplasty

The issue with PCI is even more contentious. Like CABG, PCI rates went from zero to 100,000 procedures in no time with no clinical trial to assess long-term outcomes: based just on the logic of the procedure and patients' reports of how much better they felt. Yet the first clinical trials, which appeared around early 1990s, showed no survival benefit of elective angioplasty as compared with medication. However, here the physicians took a different approach, because by the time trial results came (negative results)

Table 4: Drugs improving life-expectancy in heart failure

Drug	Mortality Reduction %	Other Benefits
ACE-I	17-37	Symptomatic benefit
ARB	Similar to ACE-I	Symptomatic benefit
Beta Blockers	34-65	Reduce hospitalizations, risk of sudden death, improve LV function, exercise tolerance; and reduce heart failure functional class
Aldosterone Antagonists	15-30	Reduction in hospitalizations and sudden death
Hydralazine/ Nitrates	43% in African Americans	Symptomatic benefit
Digoxin	No Benefit, No harm	Symptomatic benefit, Reduce hospitalization

the interventionists claimed that they had moved to next-generation devices, on the other hand the now evaluated procedure was already out-dated and therefore the trial meaningless. However, the matter-of-fact is that there are several small trials in stable CAD patients comparing PCI with medical therapy (with both single and multi-vessel disease). While most have reported only limited follow-up data they do show that PCI significantly improved angina relief and short-term exercise tolerance, but did not significantly reduce death, MI, or need for subsequent revascularization.[37-39] In fact a meta-analysis of six RCTs comprising 1,904 patients revealed that the only outcome measure that favored PCI (compared with medical therapy) was angina relief (OR 0.70; 95% CI 0.50 to 0.98). However, for death, MI, and need for repeat revascularization the ORs trended strongly in favor of medical therapy (29% to 42%) versus PCI. Further, the need for subsequent CABG was nearly 60% higher with PCI, although the situation may be slightly different when newer generation of drug eluting stents is used.[40,41] On positive side, like CABG there are certain subsets of patients where there may survival advantage with PCI particularly primary PCI. A comparative-effectiveness study of CABG surgery in a population of real-world patients (105 156 propensity score-matched Medicare patients) has shown that CABG surgery may be associated with approximately 19 days increase in life-expectancy versus PCI.[42] On the other hand, a study Berger and co-workers revealed that in those high–risk anatomic subsets in which survival is prolonged by CABG versus medical therapy, revascularization by PTCA and CABG also yielded equivalent survival over seven years.[43]

ACS / AMI

Statins

RIKS-HIA Study demonstrated that early statin (started before or at the time of hospital discharge) therapy could lead to a 25% reduction in 1-year mortality (relative risk, 0.75; 95% CI, 0.63-0.89; P = .001) in hospital survivors of AMI.[44] Even in individuals with elevated CRP (a marker of inflammation / ACS) statin therapy could lead to a gain of life expectancy; 6.6 months in male and 6.4 months in female.[45]

Aspirin

In the ISIS-2 study, the use of aspirin (162 mg chewed) in AMI was associated with nearly 1/4th reduction of vascular mortality.[46] In other ACS (Non MI) aspirin use has been associated with reduction in fatal or nonfatal MI by 50–70% during the acute phase and by 50–60% at 3 months to 3 years.[47,48]

Beta Blockers

Several prospective RCTs trials of beta-receptor blockade therapy after AMI have demonstrated an improvement in survival, primarily due to a decreased incidence of SCD.[49-51] The benefit was notable right from the beginning (in the first few months) and persisted on long-term follow-up (even up to 6 years). At follow-up, beyond a year, these studies show a 30–45% relative reduction in SCD, with an absolute sudden death incidence reduction of 1.3–6.2%. On the other hand, CHARISMA Trial showed that β-blocker use in patients with prior MI but no heart failure was associated with a lower composite cardiovascular outcome driven but no reduction in mortality. [32] The ACC/AHA committee on chronic stable angina recommends beta-blockers as the first-line therapy in post-MI patients based on evidence of improved mortality.[52]

Renin Angiotensin System

CREDO-Kyoto PCI/CABG registry cohort-2 investigators studied nearly 12,000 patients undergoing first PCI and demonstrated that patients with MI, treated with ACEI/ARB had a survival advantage: 3-year all-cause mortality (6.6% vs.11.7%, P<0.0001). However, this benefit was not manifest in non MI patients.[53]

Thrombolysis

The Fibrinolytic Therapy Trialists' Collaborative Group evaluated 9 trials including 58,600 patients and demonstrated highly significant absolute mortality reductions of about 30 per 1000 for those presenting within 0-6 h and of about 20 per 1000 for those presenting 7-12 h from onset but a (statistically) uncertain benefit of about 10 per 1000 for those presenting at 13-18 h. The benefit was observed both among patients presenting with ST elevation or bundle-branch block--irrespective of age, sex, BP, heart rate, or previous history of MI or diabetes--and was greater, the earlier the treatment began.[54] The temporal effect on survival was demonstrated in other studies as well; in a retrospective subgroup analysis of

Table 5: Disease stage and impact of various therapies in prolongation of life

Intervention	Primordial Prevention	Primary Prevention	Stable CAD	Unstable CAD	CHF	End-stage Heart Disease
Life-style intervention	+	++	+++	+++	+++	NA
Statins		±	+	++	NA	NA
ASA		±	+	++	NA	NA
ACE-I / ARB			+	++	+++	NA
Beta-blockers			±	+	+++	NA
Aldosterone Antagonists					++	±
ICD					+	+
CRT					+	+
Cardiac Assist Devices					±	+
Mechanical Ventilation						+
CPR						+

patients in GISSI-1 trial showed that patients randomized to streptokinase (or control treatment) within 1 hour of symptom onset there was a 51% reduction in mortality (studied at 21 days).[55]

Percutaneous Coronary Angioplasty

A meta-analysis of 10 randomized trials demonstrated the superiority of PTCA over thrombolytic therapy in preventing death and other adverse clinical outcomes; a reduction of mortality by more than 1/3rd (34%, P= 0.02), an absolute risk reduction for death of approximately 2%, death or nonfatal AMI (11.9% vs. 7.2%, P< 0.001), all stroke (2.0% vs. 0.7%, P= 0.007), and hemorrhagic stroke (1.1% vs. 0.1%, P< 0.001).[56]

CONGESTIVE HEART FAILURE

As life-span decreases, as a consequence of severity of disease, several therapeutic interventions may aid in bringing down the mortality.

Drugs

Several drugs may be effective in this situation and the mechanism may involve either preventing the development of lethal heart rhythms or by limiting the on-going damage to heart muscle Table 4.[57]

1. ACE-I.
2. ARBs .
3. Beta-blockers.
4. Aldosterone receptor antagonists (but not other diuretics which can improve symptoms but do not improve survival.)
5. Hydralazine/Nitrates

Beta-blockers, bisoprolol, metoprolol, and carvedilol have been shown to reduce total mortality in several studies.[58-60] The effect seems to be predominantly due to reduction of mortality from SCD (42% with bisoprolol in CIBIS II, an absolute risk reduction of 2.7% over a mean follow-up period of 1.3 years) but the effect may also be due to reduction in ischemia.[61]

The mechanism of mortality reduction with ACE- I is under scrutiny. The CONSENSUS trial showed a 31% reduction of total mortality at 1 year in the enalapril (vs. the placebo group) but no reduction in sudden death.[62] On the other hand in the TRACE study, trandolapril significantly reduced the risk of SCD in post MI patients with LV dysfunction, a 22% relative decrease and a 3.2% absolute decrease in SCD over a 4-year period.[63]

Even, aldosterone antagonists seem to significantly reduce mortality in patients with severe heart failure by reducing arrhythmic deaths. In the RALES study, over a 2-year period, the relative risk of SCD was reduced by 29%, and absolute risk reduced by 3%.[64]

Devices

COMPANION trial was a RCT comparing standard heart failure drug therapy alone, or in combination with either cardiac resynchronization therapy (CRT) or CRT plus implantable cardioverter-defibrillator (ICD) in heart failure patients - NYHA class III–IV with LVEF ≤35% and QRS width ≥120 ms. They found that mortality was reduced equally in both the device arms (with no significant improvement of mortality with combined device; CRT/ICD (combo device). Thus use of a combo device in this situation should be based on the indications for ICD therapy.[65]

Surgery

Heart transplantation is the therapy of choice for the treatment of end stage heart failure and has been shown to improve not only life-span but also exercise capacity and quality of life.[66]

In patients of dilated cardiomyopathy, heart failure and significant mitral regurgitation, there is some data which suggests that mitral valve surgery may be associated with reduction in mortality as well as improvements in quality of life.[67]

LIFE-SUSTAINING THERAPIES

Life-sustaining therapy is any intervention, technology, or treatment that forestalls the moment of death or simply those therapeutic maneuvers withholding or withdrawing them would lead to termination of life. Thus by definition these interventions have the effect of increasing the life span of the patient. Many "therapies" may qualify this category: mechanical ventilation, cardio-pulmonary resuscitation, vasoactive agents, dialysis, artificial nutrition, hydration, antibiotics, blood replacement products as well as those specific for cardiac condition such as ICDs (for secondary prevention of SCD), pacemakers (for bradyarrhythmias), and cardiac mechanical assist devices (for advanced decompensated heart failure).[68]

DRUGS OR LIFE-STYLE MODIFICATION

The efficacy of either strategy depends on the stage medical science intervenes (Table 5). Since life-style diseases now account for nearly 2/3rd of all serious diseases world-wide, a strategy targeted towards these diseases is likely to yield most results.[69]

Drugs are powerful, indispensable weapons against CVD once it develops. However, its value in prolongation of life may not be that impressive in stable conditions: In stable CAD absolute reduction of mortality with drugs is in range of 1%. The benefit of therapeutic interventions (drugs and devices), increase with severity of disease, in range of 5-10% absolute risk reduction in ACS and in the range of 10% with CHF. However, because these strategies are expensive, they certainly have at least some side effects, alone they may be not sufficient. In contrast, a healthy lifestyle is inexpensive, safe and effective.

In primary prevention risk factor modification can be a very effective strategy contributing to absolute mortality reduction in the range of 5% with a combination of all these strategies. On the other hand role of drugs (in this subset), if at all is controversial and a matter of on-going debate.

In a perfectly healthy individual (primordial prevention) the only maneuvers which seem to help are adhering to a level of health which does not permit risk factors to appear (an ideal life style), a strategy capable of reducing cardiac deaths by 90% and prolonging life-expectancy by 10 years. However, while life-style modifications are effective they are not simple to implement. It requires change and persistence (adherence to change). Thus, going beyond mere medical care, psychological and nutritional counseling, social and family support may also be required to manifest a life-time behavior modification.

CONCLUSIONS

The inevitability of death has been instrumental in search for therapy that extends life, the "elixir of life." Over the course of eons several interventions have been discovered which help in prolonging life but in a special circumstance. In general the more severe the disease and the longer the time life-saving intervention is applied the greater the benefit. PCI and CABG are more useful in sicker patients with CAD while statins, aspirin and ACE-Inhibitors are clearly beneficial in any CAD, although magnitude of benefit is still small, if any, when used in primary prevention.

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