

# Hippocratic Oath and Heart Failure Journey: An Update on Therapies

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**ABSTRACT:** The innovation that has taken place in medicine, combined with state-of-the-art technological developments, provides therapeutic options for patients in conditions that were previously considered incurable. This promotion at the same time presents us with new ethical challenges. In this article, we review the journey through life of an advanced heart failure patient, covering a variety of potential clinical and ethics subjects in the field of heart failure treatment. We review the ethical principles of the Hippocratic Oath against the background of the realities of practicing medicine and of the enormous advances in therapeutics.

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As physicians, we have to continually check that we are fulfilling the enormous obligations that we took upon ourselves as we launched into our careers to treat people while guided by the *Hippocratic Oath* to uphold specific ethical and medical standards. The original oath, written in Ionic Greek, between the 5th and 3rd centuries BCE [1], has been modified a number of times and reflects the innovations in medicine, particularly in the field of heart failure (HF). The oath, with its modifications, forms the basis of the *Oath of the Hebrew Physician*, which was composed by the neurologist Prof. Lipman Halpern. This oath has become an integral part of the graduation ceremony of all Israeli medical schools [2]. In this review, we have included sections of the oath in bold within the text.

I (YP) first became acquainted with the Hippocratic Oath as a new and enthusiastic physician, and now, following a decade as a practicing senior cardiologist in the field of HF, I review these ethical principles against the background of the realities of practicing medicine and of the enormous advances in therapeutics. I approach this task with enthusiasm and with humility, while concomitantly evaluating the course of one of the first patients I had the privilege to accompany on his journey through life.

**“I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow”**

This review article has been written at the request of the patient's first and leading physician, who saved his life several times. I have had the great privilege to follow in his footsteps. I am also fortunate to have the support of a young cardiac surgeon, bringing new and complementary insights to patient treatment.

*The story begins 26 years ago (in 1993), GA, currently 72 years old, presented with an unstable angina pectoris due to three vessel coronary artery disease (3VCAD) and underwent coronary artery bypass grafting (CABG) (left internal mammary graft to the obtuse marginal, free right internal mammary graft to the left anterior descending artery, and vein graft to the posterior descending artery).*

The optimal treatment of ischemic coronary artery disease is one of the leading, most highly debated issues in cardiology and cardiothoracic surgery today. Many significant advances in both surgery and percutaneous coronary intervention (PCI) have occurred in recent years and are the subject of numerous randomized controlled trial (RCTs) and a plethora of a retrospective studies.

The SYNTAX study, which enrolled 1800 patients, aimed to compare the relative efficacy of CABG vs. drug eluting stent (DES)-PCI (using TAXUS stents) in all-comers with severe 3VCAD or left main (LM) disease who were deemed eligible for either CABG or PCI. The results demonstrated that for patients with LM disease and/or 3VCAD, CABG (with the use of at least one arterial graft) is superior to PCI with TAXUS DES [3–11]. This finding is especially true for reducing 12-month

**Heart failure therapy is an emerging field with enormous pharmacological, technological and device innovations**

major adverse cardiac coronary event rates driven by the need for repeat revascularization in the PCI arm. CABG was, however, associated with a higher risk of cerebrovascular accident (CVA) at 12 months. The most significant benefit of CABG seems to be in patients with diabetes mellitus. Long-term results have indicated that the adverse clinical outcomes are lower with CABG

compared with PCI, due to a reduction in repeat revascularization, myocardial infarction (MI) and MI-related mortality. Cost effectiveness analyses also demonstrate a benefit with CABG over PCI at 5 years, but in patients with LM disease and low SYNTAX scores, PCI was the dominant strategy. From a quality-of-life endpoint, CABG was better than PCI regarding the incidence of recurrent angina.

The BEST [12] and FREEDOM [13] trials showed the same superiority, irrespective of the SYNTAX score. A large patient-level meta-analysis, combining the results of SYNTAX and BEST trials, concluded that CABG offers improved outcomes when compared to DES-PCI in both diabetics and non-diabetics and in multi-vessel disease (2 or 3 VACD involved) with proximal LAD involvement [14].

*Six years later (1999), GA presented with type A aortic dissection [Figure 1] and underwent urgent surgery that included ascending aorta replacement with a Dacron graft and reimplantation of the patent grafts, with preservation of the aortic valve. He was left with chronic aortic dissection down to the renal arteries.*

Acute type A aortic dissection is a rapidly developing fatal disease with high mortality and morbidity rates. Sixty percent of patients treated conservatively die within 30 days, mostly due to tamponade, rupture, or end organ ischemia [15,16], and therefore these patients undergo immediate surgical intervention [17,18]. Currently, improved surgical techniques and new technologies have led to a decline in mortality rate of 13–17% [19,20].

**“I will not be ashamed to say ‘I know not,’ nor will I fail to call in my colleagues when the skills of another are needed for a patient’s recovery”**

**Figure 1.** Computed tomography angiography showing dissection of the aortic arch



### The enormous advance in therapeutics raises new ethical challenges

*During the following years, GA devolved severe symptomatic aortic regurgitation. Echo showed moderate-severe reduced left ventricular (LV) function (ejection fraction [EF] 30%). He experienced moderate dilated LV size (LV end diastolic diameter of 6.6 cm/LV end systolic diameter of 5.3 cm), mildly reduced right ventricular function, moderate functional mitral regurgitation, and mildly increased pulmonary artery pressure. Aortic annulus was measured by transesophageal echocardiogram and found to be 28 mm with no valvular calcifications. Computed tomography angiography showed a caliber of > 7 mm of the left axillary artery with documented continuation with true lumen of the ascending aorta and aortic arch.*

This stage of the case illustrates the Heart Team concept that has been developed to integrate evidence-based medicine and a multidisciplinary approach to decision making regarding aging demographics in the rapidly evolving field of cardiovascular medicine. Although transcatheter aortic valve implantation (TAVI) is indicated only for patients with severe symptomatic calcific aortic stenosis, it has been used in a number of additional valvular pathologies for the no-option patient. Given the patient history of two open heart surgeries, biventricular dysfunction, and the persistent aortic dissection involving the aortic arch and the descending aorta, a Heart Team decision supporting off-label TAVI was made, resulting in a trans-axillary implantation of a 29 mm CoreValve™ (Medtronic, USA) [Figure 2]. The patient recovered well, resumed his regular physical activities, and returned to New York Heart Association (NYHA) functional class I [21].

Consistent with the Hippocratic Oath, in patients in whom there is anatomical or clinical equipoise, the Heart Team approach should be implemented for complex decision making to achieve best clinical outcomes [22].

**Figure 2.** Transaxillary CoreValve™ (Medtronic, USA) implantation for severe aortic regurgitation



**“I will prevent disease whenever I can, for prevention is preferable to cure”**

*Despite the above improvement, ventricular function did not recover following TAVI. The patient showed deteriorating severe dilatation of LV and severe mitral regurgitation, followed by clinical deterioration, with an electrocardiograph (ECG) pattern of left bundle branch block (LBBB) with QRS duration of 130 ms.*

Several practice-influencing studies, bringing advances along many frontiers in HF, have recently been reported, as described below.

In the past few decades, statins have played a substantial role in the management of cardiovascular disease for both primary and secondary prevention. Yet, a beneficial prognostic impact of statins has not been established definitively in patients with HF, and the subject remains controversial. A recent large prospective study (CHART-2) showed that statin use was associated with a beneficial prognosis in HF patients with ischemic heart disease. Of note, in that study, statin administration was particularly associated with favorable outcomes in HF patients with borderline or preserved EF but not in those with reduced EF, LV dilation, hypertrophy or higher NYHA classes [23].

The best treatment for chronic mitral regurgitation that is secondary to severe LV dysfunction is another subject that has remained controversial, and it is unclear whether correction improves clinical outcomes compared with guideline-recommended medical therapy and cardiac resynchronization therapy (CRT). Two recently published randomized clinical trials assessing the utility of percutaneous transcatheter repair with the MitraClip device (COAPT [24], MITRA-FR [25]) demonstrated variable results further emphasizing the controversy regarding the optimal strategy for this patient population.

CRT has been shown to reduce morbidity and mortality in certain patients with systolic HF. Despite the general consistency of international guideline recommendations, there are still certain patient populations for whom there are variations in recommendations concerning eligibility for CRT, and selection of the most appropriate device for the particular patient remains open to question. In LBBB patients with narrower QRS duration (120 to 149 ms), there is a particular lack of agreement, especially in those with a QRS duration < 129 ms and NYHA functional class II symptoms. A striking discrepancy exists between the European Society of Cardiology guidelines and those of the European Heart Rhythm Association providing a Class I recommendation for QRS duration between 120 and 129 ms and NYHA class III [26].

*In light of all the clinical and therapeutic considerations, GA underwent a CRTD implantation, but without significant clinical improvement.*

**“I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon’s knife or the chemist’s drug”**

*Nine years following TAVI implantation, clinical deterioration continued, progressing to NYHA functional class III, despite the optimal medical therapy practiced. Echo at this stage showed severe biventricular dysfunction with severe dilated LV, severe pulmonary hypertension, paravalvular aortic leak and severe mitral regurgitation [Figure 3].*

The calcium sensitizer and potassium channel-opener levosimendan is an inotropic drug with three major mechanisms of action: positive inotropy, vasodilation, and cardio-protection. Published data have shown the potential advantages of levosimendan in the management of acute decompensated HF and advanced HF when standard medical therapies threaten hemo-

dynamics and organ perfusion is unable to alleviate clinical symptoms. Intermittent or repeated courses of levosimendan have been associated with reduced HF-related hospitalizations and an improved heart-related quality of life. In a number of meta-

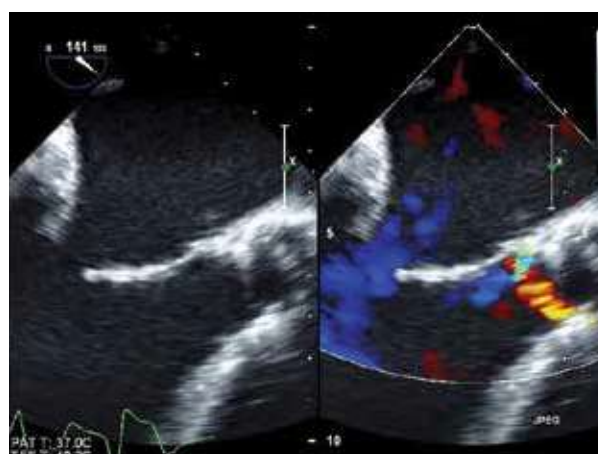
analyses, a survival benefit from levosimendan compared with conventional inotropes was reported [27]. At present, validation of these findings in large controlled trials remains elusive.

*At this stage intermittent levosimendan therapy was initiated, in the cardiology department, which had become his second home. Despite the lack of significantly improved BNP levels or echocardiographic parameters, there was significant clinical improvement.*

It is commonly accepted that under the right circumstances a placebo – the idea that your brain can convince your body

### Physicians face enormous obligations, which are guided by the “Hippocratic Oath”, to uphold specific ethical and medical standards

**Figure 3.** Transesophageal echocardiography showing a paravalvular aortic regurgitation





a fake treatment is the real thing – can be just as effective as traditional treatments. Recent research has demonstrated that the placebo effect is a genuine psychobiological phenomenon attributable to the overall therapeutic context, and that placebo effects can be robust in both laboratory and clinical settings. Evidence has also emerged that placebo effects can exist in clinical practice, even if no placebo is given [28].

*Observation of the patient on his arrival for this treatment, taking note of interpersonal relationships and the projected sense of security, were undoubtedly major contributing factors to the improvement in his condition.*

**“I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know. Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God”**

*With GA aged 72, facing end-stage HF, moderate-severe renal dysfunction (estimated glomerular filtration rate of 35) and chronic aortic dissection, I kept seeking a cure.*

Heart transplantation (HT) is the gold standard life saving therapy for end stage HF patients, and has been practiced for more than 50 years. With the increasing number of elderly patients being referred for cardiac interventions, cardiologists and cardiac surgeons are faced with evaluating older patients, with end-stage heart disease not amenable to further medical or conventional cardiovascular surgical therapy for HT. While the upper maximum age for HT was initially 55 years, the age limit is currently undefined [29]. UNOS data reveals that 11.7% of transplantations in 2008 were in patients over 65 years, up from 2.1% only 10 years earlier [30]. Patients over 65 years are currently the third largest age group for transplantations, after 50–64 years and 35–49 years. Yet many HT programs still exclude patients older than 65 years due to concern that advanced age is a risk factor for morbidity and mortality. Given the scarcity and limitation of this treatment opportunity there are major medical, ethical, and legal issues yet to be resolved. Medico-ethical and moral considerations include the questions [31]: Should an older patient deserve to be considered for HT in light of the prevailing shortage of donor organs? How old is too old for HT? Can elderly patients sustain the rigors of transplantation, can they be rehabilitated and lead a productive life? Do they deserve suboptimal or potentially compromised donor organs? Should they “jump ahead” of younger patients on the transplant list if their condition deteriorates? Is transplantation cost effective? And most importantly, do they do as well in the long term as younger patients?

*Given advanced renal failure, GA was presented for various HT programs around the world for heart and kidney transplantation, but was excluded from this therapy.*

**“I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism”**

In the last decade, the use of mechanical circulatory support (MCS) has increased rapidly [32]. Established indications for MCS include, further to bridge-to-transplant, also destination therapy (i.e., lifetime use of devices in transplant ineligible patients) [33]. Although early devices improved prognosis, there was a high risk of adverse events, including pump malfunction due to pump thrombosis [34]. The fully magnetically levitated centrifugal continuous-flow circulatory pump, HeartMate 3 LVAD (Abbott, USA) was designed to reduce shear stress on the blood and consequently to reduce the risk of pump thrombosis [35]. The recent MOMENTUM 3 trial was conducted assess the HeartMate 3™ in patients with advanced HF refractory to standard medical therapy [35]. The study demonstrated that the composite of survival free from disabling stroke or survival free from reoperation to replace or remove a malfunctioning device was significantly increased in patients randomized to HeartMate 3 compared with the axial-flow pump HeartMate II™ LVAD (Abbott, USA). The HeartMate 3 device was therefore deemed superior in terms of reducing complications associated with LV assist systems.

*With prior two open heart surgeries, advanced chronic renal failure, chronic aortic dissection, valvular and paravalvular leak of aortic artificial valve, background of factor VII deficiency, the therapeutic option of MCS was disqualified.*

**“I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person’s family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick”**

*Throughout the stages of therapy, particularly at the critical decision-making junctions, GA participated in the decisions, evaluating the recommendations and therapeutic decisions and fully understanding the consequences, both good and devastating, associated with each of the therapeutic choices, while keeping in mind that each therapeutic option had a direct impact on his family, economic situation and immediate environment.*

Autonomy, as one of the basic principles of healthcare ethics, reflects the patient’s right to independence in thought, intention, and action in their own healthcare decision making. For a patient to make a fully informed decision, they must be advised



of all the risks and benefits of the procedure and the likelihood of success.

HF is a complex, relapsing, severe, chronic disease leading to multisystem dysfunction, unfavorably comparable to many malignant conditions. Multidisciplinary team (MDT) care is often part of disease management programs, with MDT being a term covering a broad range of structured treatment plans and interventions for patients with chronic disease [36]. The aim is to provide individualized, holistic care that is responsive to the changing needs of patients throughout the course of the illness and to seamlessly transition primary and secondary care. In other words, it allows patients to receive the right care from the right person at the right time. The ideal MDT members should include: HF physician specialist, HF nurse specialist, general practitioner/primary care doctor, pharmacist, physiotherapist, palliative care specialist, psychologist, occupational therapists, and administrators. The most up-to-date meta-analysis assessing MDT outcomes has shown a significant reduction in mortality and HF hospitalizations with MDT care [37].

**“I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm”**

HT is restricted by donor heart availability, the extraordinary gift of life of those unfortunate young people who died unexpectedly. A huge demand for organs and massive profits drive a thriving illegal organ trade. Over the years we have witnessed many unethical acts, notable among them is the use of organs from executed prisoners, violating every basic human right, medical ethics, and international conventions [38]. In stark contrast, Dr. Janusz Korczak stands out as a representative of all that is noble in the human heart. Physicians have a special responsibility in our society, and an obligation to all people, to treat with respect, dignity and care, regardless of the circumstances.

## CONCLUSIONS

The ethical principles of the Hippocratic Oath continue to guide physicians throughout the world millennia after they were introduced.

**“If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter. May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help”.**

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## Capsule

### Mouse mothers transfer metabolic mode

Obesity and metabolic diseases tend to go together, and humans who become obese are also prone to type 2 diabetes and cardiovascular problems. Starting with the observation that offspring of germ-free mice tended to become obese on high-fat diets, Kimura et al. investigated how the presence of the microbiota might be protective in mice. Short-chain fatty acids (SCFAs) from the microbiota are known to suppress insulin signaling and reduce fat deposition in adipocytes. Further experiments showed that SCFAs in the bloodstream were able to pass from a non-germ-free mother's gut microbiota across

the placenta and into the developing embryos. The authors found that in the embryos, the SCFA propionate mediates not only insulin levels through GPR43 signaling but also sympathetic nervous system development through GPR41 signaling. A high-fiber diet promoted propionate production from the maternal microbiota, and maternal antibiotic treatment resulted in obese-prone offspring.

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Eitan Israeli

## Capsule

### Invasive infections with fungi after organ transplantation and chemotherapy

Invasive infections with fungi like *Candida albicans* can be a serious complication of organ transplantation and chemotherapy. One possible explanation is that these procedures alter the intestinal microbiota, which may provide an opening for opportunistic fungi. For better insight into this relationship, Zhai et al. investigated patients receiving allogeneic hematopoietic stem cell transplants. They used high resolution mycobiota and microbiota sequencing of recipients' blood and feces to track the dynamics of infection.

A pronounced loss of bacterial microbiota and diversity (especially of anaerobes) was accompanied by expansion of pathogenic *Candida* species in the intestine. This overgrowth in the gut preceded bloodstream *Candida* infections. In the future, similar monitoring approaches may be used to better target patients at risk for invasive fungal infections.

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Eitan Israeli

**“The successful revolutionary is a statesman, the unsuccessful one a criminal”**

Erich Fromm (1900–1980), psychoanalyst and author