Pharmaco-invasive vs. facilitated percutaneous coronary intervention strategies for ST-segment-elevation acute myocardial infarction patients in the new ESC Guidelines

Reviewed by Frans Van de Werf, ESC Guideline Committee chairman

The role of percutaneous coronary interventions (PCIs) in the early hours of an ST-segment-elevation acute myocardial infarction (STEMI) can be divided into primary PCI, PCI combined with pharmacological reperfusion therapy, and ‘rescue PCI’ after failed pharmacological reperfusion.

Primary PCI can be defined as coronary angioplasty/stenting without prior administration of fibrinolytic agents or GPIIb/IIIa antagonists. These patients are usually treated with aspirin, a loading dose of clopidogrel together with heparin or bivalirudin, before the intervention. Facilitated PCI is defined as a pharmacological reperfusion treatment delivered prior to a planned PCI, in order to bridge the PCI-related time delay. With this strategy it is important to emphasize that the decision to perform PCI is already taken before the additional pharmacological reperfusion treatment has been started. Full-dose lytic therapy, half-dose lytic therapy with a GPIIb/IIIa inhibitor, and GPIIb/IIIa inhibitor alone have been tested for this indication. There is no evidence of a significant clinical benefit with any of these agents. In spite of pre-PCI coronary artery patency rates being higher with lytic-based treatments, no mortality benefit, but more bleeding complications, was observed. The pre-PCI patency rates with upfront abciximab or high-bolus dose tirofiban alone were also not higher than with placebo, but more complete ST-segment resolution and/or a higher myocardial blush grade at angiography (but no clinical benefit) were observed with this strategy.

It is unclear why all these trials have failed to show a benefit for the patient.

In the case of full-dose lytic treatment, suboptimal antithrombotic co-therapy (e.g. no upfront clopidogrel) and recruitment of patients many hours after the onset of symptoms (and therefore a reduced chance to save more ischaemic myocardium) have certainly played a significant role. One might question whether upfront administration of a GPIIb/IIIa antagonist followed by PCI should be considered facilitated PCI in the absence of improved patency in the infarcted artery. A pharmaco-invasive strategy can be defined as pharmacological reperfusion (using fibrinolytic agents) with an ‘invasive back-up’, which means that patients are transported to a PCI hospital for either immediate rescue PCI in case of failed fibrinolysis or non-urgent coronary angiography to determine the need for additional treatment of the culprit lesion (PCI or bypass surgery). This strategy has been shown to be superior to a very conservative approach of in-hospital fibrinolysis with transfer to a PCI centre only in case of failed thrombolysis.

The new ESC guidelines recommend the performance of a coronary angiogram 3–24 h after successful thrombolysis (>50% resolution of ST-segment elevation, reperfusion arrhythmia, disappearance of chest discomfort). This time window is justified, on the one hand, by the fear of thrombotic complications when an intervention is performed immediately following the administration of the lytic agent due to its prothrombotic effects and, on the other hand, of spontaneous re-infarction which is much more frequent in the first days following lytic therapy.

Primary PCI within the recommended guidelines time window cannot be offered to all patients, not even with a well-functioning network of ambulances and hospitals. For some of these patients, especially those presenting very early without an increased risk of bleeding, immediate lytic therapy (in the ambulance or the emergency department of the community hospital) is still the best treatment, provided they can be transferred to a PCI hospital for rescue PCI, or for angiography, in order to decide on final treatment of the culprit lesion (PCI, bypass surgery or in some cases no mechanical treatment). Ideally, these patients should be transported to the PCI hospital immediately after starting lytic therapy. On arrival at the PCI hospital, a new ECG should be taken and the decision made to perform angiography either immediately or within 24 h.

Reference: current ESC STEMI Guidelines.

Andras Tofield
The Cardiologist as a writer: thoughts about and within everyday medical practice

Cardiologists write a lot about Cardiology and a few on other topics. Here, Thomas Lüscher a prominent cardiologist discusses his recently published book, *Thoughts of and about Medicine.*

Cardiologists write a lot: mainly reviews, papers, guidelines, and mails. Life is hectic in cardiology, the field is on the move: every other month sees a new stent developed, a new molecule tested, every other year a new procedure is introduced. Cardiologists themselves are on the move, sorting presentations, answering mails, in planes from one meeting to another. Shrinking of the present is particularly dominant in this specialty. It leaves little room for more contemplative thoughts, thoughts about the meaning of life, health, and medicine, where it came from, and where it is going.

The editor-in-chief of the *European Heart Journal* Thomas F. Lüscher, before accepting his new and demanding job, barely found time to think about things behind the noise of daily activities—yet managed to write a book about medicine, its origins, and what it means today as well as about the science of medicine and how it developed, about physicians and how they think and interact and, eventually, about health, disease, and death.¹

Philosophers used to cover such issues, and indeed philosophy is a past passion of the author. As a young man unsure of what to do in life, he initially studied—in order to delay the decision—philosophy and medicine in the early seventies at the University of Zurich. Philosophy eventually was not enough for life, but after a quarter of a century of experience as a practising physician and cardiovascular scientist, the questions come back.

Gedankenmedizin—a pun in German referring to thoughts as medicine and thoughts about medicine—is an unusual and personal book. Its 16 chapters assembled in four sections cover a variety of topics behind the everyday life of a doctor.

The first, entitled, So far (‘bis anhin’) is a journey from the symbol to the organ and how our thinking evolved from myths to scientific reasoning. The heart offers itself particularly well for such an essay, as it represents the symbol of life that with the rise of modern science has transformed it into an organ.

The second, devoted to reflections on how we think, talk, and act as scientists (‘Innensicht’) addresses the issue of whether medicine is a science or an art, what the grounds of knowledge are, and how we can or cannot translate it into recommendations for clinical practice. Examples of how knowledge developed—mainly by error rather than planned, are described: the transformation of an explosive into a biological mediator (nitroglycerin), and the understanding of bleeding and thrombus formation illustrated by famous patients such as the Tsarevitch, Eisenhower, and Thomas Mann (pantarei).

The third topic addresses external viewpoints (‘Aussensicht’): the perception of medicine and physicians by the media, which has undergone a change from admiration to suspicion towards clinical and academic activities. Also the relationship of medicine to its academic neighbour, the humanities.

Importantly, conflicts of interest as they are perceived by the public, politicians, and media are discussed, and a less hypocritical approach is proposed than in current practice.

A special chapter (‘How are you?’) is devoted to the USA and the transatlantic gap as perceived by a visiting scientist from old Europe.

The final section, called Outlook (‘Voraussicht’), addresses the inflation of diagnoses in medicine and—as a consequence—the paradoxical shrinking of health. The redirection of medicine, from relieving pain and treating of disease to perfection, leads to thoughts about its true aims and deeper meaning, which are discussed in the last chapter that leads us back to the grounds of the profession in the age of genes and stem cells (Meta-Medizin).

This unusual book that has been introduced and launched in October at the Frankfurt Book Fair (Buchmesse) 2009 raises a lot of questions and gives no final answer. It stimulates the reader to do what the title suggests—to think about the meaning of this fascinating profession that rose from myth to science.

A. Tofield

Reference

Valsartan reduces morbidity and mortality in Japanese patients with high-risk hypertension, reported the KYOTO HEART study in the Hotline III session of the ESC 2009 meeting.

‘The KYOTO HEART study confirms that the angiotensin receptor blocker valsartan exerts an overall cardiovascular protective effect in high-risk Japanese hypertensive patients and in particular exerts anti-stroke and anti-angina actions’, said the presenter Hiroaki Matsubara, from Kyoto Prefectural University of Medicine (Kyoto, Japan).

The KYOTO HEART study—which took place in Japan between January 2004 and January 2009—was designed to determine whether the evidence found in Western countries for benefits of blockade of the rennin–angiotensin system might be directly applied as a long-term strategy for East Asian populations, including Japanese. Few previous studies to date have included Asian populations.

In the study, 3031 Japanese patients with uncontrolled hypertension (defined as BP ≥140/90 mmHg) and one or more additional cardiovascular risk factors (including a history of CV events, diabetes, smoking habit, dyslipidaemia, obesity, and left ventricular hypertrophy) were randomly assigned to the add-on valsartan arm (n = 1517; where valsartan was initiated at a dose of 40–80 mg and titrated up to 160 mg, if necessary) or the non-ARB optimal antihypertensive treatment (n = 1514).

At 3.27 years, the primary endpoint (defined as a composite of fatal and non-fatal cardio or cerebrovascular events) was reduced from 10.2% in the non-ARB arm (155 patients) to 5.4% (83 patients) in the valsartan arm (HR 0.55, 95% CI 0.42–0.72, P = 0.00001). Furthermore, lower rates of stroke (1.7 vs. 3.0%, HR = 0.55, P = 0.01488) and angina (1.5 vs. 3.0%, HR = 0.51, P = 0.01058) also occurred in the valsartan-treated group. The study was terminated prematurely for ethical reasons when unequivocal benefits were observed in the valsartan treatment group.

Discussant Frank Ruschitzka (Zurich University Hospital, Switzerland) commented that the results ‘were impressive, almost too good to be true’, adding that the 45% risk reduction in the primary endpoint, 45% risk reduction in stroke, and 49% risk reduction in angina were ‘diametrically’ different from the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial. The different results of VALUE and KYOTO, he suggested, might be explained by the study populations, with Asians being particularly receptive to the protective effects of ARBs.

In answer to the question of whether ARBs have come of age, Ruschitzka said: ‘The answer, with regard to safety and efficacy, could be a resounding yes, i.e. if efficacy were determined as blood pressure reduction. However, blood pressure is merely a surrogate endpoint which correlates to some extent with the true endpoint, namely heart attack, stroke, and death. . . . ARBs are efficacious and even superior to other drug classes in stroke prevention but their efficacy with regard to coronary events remains uncertain’.

Despite the initial promise of the PROTECT pilot study, the larger PROTECT trial—presented in the Hotline III session at the ESC 2009 meeting—showed no difference with respect to both primary and secondary endpoints between rolofylline and placebo.

‘Although there was a pharmacological basis on which to expect improvement, the benefits seen in a small pilot trial, as frequently happens, could not be replicated in a larger trial’, commented Marco Metra, the presenter of the study from the University of Brescia (Brescia, Italy).
Patients hospitalized with acute decompensated heart failure (ADHF) often develop worsening of their renal function (WRF) and reduced diuretic responses during treatment, a clinical problem that has been associated with longer hospital stays and worse inpatient and post-discharge clinical outcomes.

The PROTECT (Placebo-controlled Randomized study of the selective A1 adenosine receptor antagonist KW for patients hospitalized with acute HF and volume Overload to assess Treatment Effect on Congestion and renal function) Trial was designed to assess whether treatment with selective adenosine A1 antagonists (A1RA) can enhance diuresis and prevent WRF.

Earlier, the PROTECT-Pilot study, which had involved the randomization of 301 patients treated with rolofylline 30 mg, showed that treatment was associated with trends towards better symptom improvement (a potentially favourable effect on dyspnoea), less WRF, and fewer deaths or readmissions for heart failure or renal dysfunction.

In the larger PROTECT study, 2033 patients hospitalized for HF within 24 h with signs of fluid overload, and impaired renal function (estimated GFR 20–80 mL/min) and high BNP or NT-proBNP plasma levels (>500 pg/mL or <2000 pg/mL, respectively) were randomized 2:1 to rolofylline 30 mg per day (n = 1356) or placebo (n = 677) administered as a daily infusion for 4 h daily over 3 days.

Analysis showed that the primary endpoint of treatment success was achieved in 36.0% of patients in the placebo group vs. 40.6% in the treatment group, and that treatment failure occurred in 19.8% of the placebo group vs. 21.8% in the treatment group (OR = 0.92, 95% CI = 0.78–1.09, P = 0.348).

There were also no significant differences between the treatment groups in either secondary endpoint. Dyspnoea improvement occurred in 44.5% of patients in the placebo group vs. 51.2% in the treatment group, whereas persistent renal impairment occurred 15% in the rolofylline group and 13.7% in the placebo group (P = 0.441).

Serious adverse events occurred in 13.8% of rolofylline patients vs. 14.7% of placebo patients. There was a trend towards a lower incidence of adverse cardiac events with rolofylline, but a higher rate of neurological events, specifically seizures (0.8 vs. 0%), a known adverse effect of A1 receptor antagonists, and strokes (1.2 vs. 0.5).

Clinical trial update II: TRITON-TIMI 38 provides reassurance on concomitant use of proton pump inhibitors and thienopyridines

Data from the TRITON-TIMI 38 trial—presented in the Clinical Trial Update session II at ESC 2009—provided reassurance that there is no further need for concern about interactions between proton pump inhibitors (PPIs) with clopidogrel, prasugrel, and other thienopyridines.

‘The current findings do not support the need to avoid concomitant use of PPIs in patients treated with thienopyridines’, said the presenter Michelle O’Donoghue from the Brigham and Women’s Hospital (Boston, USA).

Proton pump inhibitors are often prescribed to patients in combination with thienopyridines to reduce the risk of gastrointestinal bleeding, a strategy that is endorsed by the existing guidelines. But several studies have raised concerns that PPIs could negate the clinical benefit of thienopyridines by inhibiting CYP2C19 and thus preventing the conversion of clopidogrel to its active metabolite.

In the TRITON-TIMI 38 study, involving 13 608 acute coronary syndrome patients undergoing planned PCI who had been randomized to prasugrel or clopidogrel, 4529 (33%) participants were known to be on a PPI at the time of randomization. In the protocol, PPI usage was left to the discretion of the treating physician, with their decisions captured on case-report forms.

After adjustment for potential confounders, the authors found no significant association remaining between use of a PPI and the risk of the primary endpoint, both for patients treated with clopidogrel (HR 0.94, 95% CI 0.80–1.11, P = 0.46) and those treated with prasugrel (HR 1.00, 95% CI 0.84–1.20, P = 0.97). Furthermore, use of a PPI was not associated with increased risk of MI, stent thrombosis, or a decreased risk of bleeding for patients treated with either clopidogrel or prasugrel.

Discussant Kurt Huber from Wilhelminenspital (Vienna, Austria) said that while the TRITON-TIMI 38 analysis was more reliable than other registries and meta-analyses that had previously been published in the area, he remained sceptical about whether the study had fully resolved the issue of PPI and thienopyridine interactions. ‘Only a prospective randomized trial of PPI use will be capable of establishing the safety of PPIs in combination with thienopyridines’, he said.
Clinical trial update II: Jupiter Trial, rosuvastatin has greater efficacy in elderly populations

Using statins in adults aged 70 years and over with normal LDL-cholesterol levels, but with systemic inflammation, significantly reduced the risk of cardiovascular morbidity and mortality, reported the JUPITER trial. The latest sub-analysis, presented in the Clinical Trial Update II session at the ESC 2009 Annual meeting, suggests elderly patients have the potential to derive even greater benefit from rosuvastatin treatment than younger populations.

The use of statins in elderly populations has been controversial since the drugs are thought to decrease in efficacy with age, despite older patients being at higher risk of suffering cardiovascular events.

JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) is a large, multinational, long-term, double-blind, placebo-controlled, randomized clinical trial that has been designed to assess whether statin therapy should be given to apparently healthy individuals with normal LDL-cholesterol, but raised C-reactive protein levels (defined as ≥2.0 mg/dL). The overall results of the study were presented at the American Heart Association in November 2008. Of the 17,802 men and women randomized to rosuvastatin 20 mg or placebo in the main study, a subset of 5,695 were aged 70 years or older, and therefore eligible for consideration in the latest analysis.

Results of the subset analysis of patients aged 70 years or older show that when compared with patients being treated with placebo, those on rosuvastatin treatment had a 39% reduction in the risk of experiencing the primary endpoint (defined as the combined risk of cardiovascular death, non-fatal MI, non-fatal stroke, unstable angina, and the need for revascularization; \( P < 0.001 \)).

Furthermore, when compared with patients being treated with placebo, those on rosuvastatin treatment had a 31% reduction in the risk of experiencing death (\( P < 0.001 \)); a 45% reduction in the risk of experiencing an MI (\( P = 0.046 \)); and a 45% reduction in the risk of experiencing a stroke (\( P = 0.023 \)).

Commenting on the results, the presenter Robert J. Glynn from Brigham and Women’s Hospital (Boston, MA, USA) said that it would be necessary to treat 19 people over the age of 70 to prevent one primary event, compared with having to treat 29 patients under the age of 70 to prevent one event.

Discussant Gabriel Steg from Centre Hospitalier Bichat-Claude Bernard (Paris, France) said that the elderly patients in JUPITER were on average just 74 years old, leaving unanswered the question of whether the study’s findings could be extended to individuals older than 80 years. In addition, he said, it was unknown whether there might be benefits for those without high C-reactive protein.

Janet Fricker

Obama’s research funding boost for medicine

Scientific research in the USA has received an unprecedented funding boost. Elizabeth Nabel, MD, Director of the National Heart, Lung, and Blood Institute talks to J. Taylor, MPhil, what this means for medicine.

This year the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (NIH) received a 3.2% budget increase, with funding coming in at around $3 billion (Table 1). It amounts to about 10% of the NIH budget of around $30 billion, which was uplifted by 3.7% overall.

The ARRA was signed into law by President Obama on 17 February 2009. All funds must be obligated by September 2010, but the NHLBI plans to spend as much of it as possible during the 2009 financial year.

President Barack Obama and Vice President Joe Biden host a ‘Roadmap to Recovery’ meeting with the Cabinet in the State Dining Room, 8 June 2009. (Official White House Photo by Pete Souza.)

Of the $10.4 billion allocated to the NIH through the Recovery Act, $7.4 billion will go to NIH Institutes and Centres to support scientific research. The NHLBI will receive $763 million, which is about 10% of the funds allocated to the NIH Institutes or Centres, an amount that is proportional to the NHLBI’s appropriation level.

‘The recent ARRA legislation provides an unprecedented level of funding—$8.2 billion in extramural funding—to the NIH to help stimulate the US economy through the support and advancement of scientific research’, says Dr Elizabeth Nabel, Director of the NHLBI.

But how will the funding be used? She says: ‘While NIH Institutes and Centers have broad flexibility to invest in many types of grant programmes, they will follow the spirit of the ARRA by funding projects that will stimulate the economy, create or retain jobs, and have the potential for making scientific progress in 2 years’.

That means funding new research projects; accelerating the tempo of ongoing science by supplementing current grants; and embarking on new activities that meet the goals of the ARRA, such as the NIH Challenge Grant programme.

The NHLBI intends to invest its ARRA funding in research that advances basic discoveries of the causes of diseases, promotes the translation of the basic discoveries into clinical practice, and fosters training and mentoring of emerging scientists and physicians, says Dr Nabel. She adds: ‘The Institute’s funding plan strikes a balance between increasing the number of investigator-initiated research grants and supporting its commitment to signature projects’.

All ARRA awards will come with special reporting requirements that demonstrate how the project meets the objectives of the Recovery Act.

A breakdown of the types of research projects that will be funded can be found at http://www.nhlbi.nih.gov/recovery/index.htm. They include the 2 year Research and Research Infrastructure ‘Grand Opportunities’ or ‘GO’ grants, which will support projects that address large, specific biomedical and biobehavioural research.

Dr Nabel says: ‘Research supported by the GO grants programme should provide a high short-term return and offer a high likelihood of enabling growth and investment in biomedical research and development, public health, and health care delivery’.

The NIH Challenge Grants is a new programme aimed at supporting research that addresses scientific and health research challenges in biomedical and behavioural research and would benefit from significant 2 year jumpstart funds.

High-priority topics include biomarker discovery and validation; the clinical and mechanistic link between diabetes mellitus and cardiovascular disease in low- and middle-income countries; treatment of heart failure with preserved systolic function; implantable-cardioverter defibrillators and cardiac resynchronization therapy in heart failure; screening for cardiovascular risk factors in children; cost-effective trials of cardiovascular disease prevention in people with low short-term risk; using existing data sets to plan effectiveness trials in paediatric cardiology; treatment of stenosed coronary arteries with hybrid coronary revascularization vs. multi-vessel percutaneous intervention with drug-eluting stents; cost-effective strategies to achieve smoking cessation in hospitalized patients with cardiovascular disease and COPD; and developing cell-based therapies for cardiovascular, lung, and blood diseases.

Eligibility to apply depends upon each specific ARRA programme. Specific details can be found for each topic at http://www.nhlbi.nih.gov/recovery/nhlbiarra.html.

### Table 1 NIH fiscal year 2009 enacted appropriations US$

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Source: http://officeofbudget.od.nih.gov/pdfs/FY09/FY%202009%20Enacted%20Appropriations%20(Final).pdf
The NHLBI’s vision is to provide global leadership in research, training, and education programmes to stimulate basic discoveries about the causes of disease, speed the translation of basic discoveries into clinical practice, foster training, and mentoring of emerging scientists and physicians, and communicate research advances to the public.

Dr Nabel says: ‘The additional funding provided through the Recovery Act will help the NHLBI accelerate progress to promote the prevention and treatment of heart, lung, and blood diseases—diseases that include three of the four leading causes of death in the United States—to enhance the health of all individuals so they can live longer and more fulfilling lives’.

She adds that the Recovery Act funds will enhance the NHLBI’s ability to strengthen its ongoing commitment to support comparative effectiveness research, which includes topics such as treatment of atrial fibrillation, reducing cardiovascular risk in moderate-risk and asymptomatic patients, and optimizing anti-platelet treatment after revascularization procedures.

‘Also known as patient-centered research, this type of research provides essential evidence to help inform health care decisions by clinicians, patients, and others based on an individual patient’s needs and preferences’, she says.

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**Sabina A. Murphy: the new Statistical Editor for the European Heart Journal**

S.A. Murphy MPH, recently joined the EHJ from the Brigham & Women’s Hospital TIMI Study Group, Boston, where she worked closely with cardiologists.

The area of statistics in research does not exist in a vacuum. Too often, statistics is seen as a separate field unrelated to cardiology. Some have called statistics a ‘necessary evil’ in research. However, not everyone sees it that way.

Ms Murphy acquired first-hand experience of the interface between statistics and cardiology as the director of biostatistics at the TIMI Study Group for 10 years, a clinical trial group chaired by Eugene Braunwald, MD.

‘So much of what cardiologists do on a day-to-day basis is influenced by statistics. What procedures are performed, what medications are approved, even lifestyle interventions have been studied in clinical trials and research. However, without the proper study design, statistical analysis, and interpretation, it is not possible to provide the information needed for clinicians to make the proper decisions’.

But it is also not possible for a statistician to select the appropriate test and draw the correct conclusions from an analysis if one does not have an understanding of what the data mean in a clinical sense, as well as from a statistical approach.

‘Handing over a database of information that has been collected to a statistician and asking them to give back the “results” without any background on what the data mean often leads to incorrect analyses or conclusions. Luckily, I was fortunate to collaborate with a group of cardiologists who spent time teaching the clinical aspect of the research. This blending of the clinical and statistical arenas impacted the magnitude of our efforts’, says Ms. Murphy.

Likewise, statisticians should explain their methods and results to the researchers in a manner that can be understood. ‘It really should be a two-way street’, she says.

In addition to her work with the TIMI Study Group, Ms Murphy was also the associate editor for clinical trials for the American College of Cardiology website Cardiosource.com. In that role, she wrote more than 600 trial summaries from cardiology manuscripts and late-breaking trial presentations at the major cardiology meetings.

Previously Ms Murphy spent 2 years working with the National Institute on Drug Abuse (NIDA) tracking emerging drug abuse patterns using community level data. She completed her graduate work at the Johns Hopkins University School of Public Health.
Progress in the development of an artificial heart

Once unimaginable, a functional artificial heart now exists as a temporary short-term bridge while waiting for a donor organ. Diana Berry, MA, reviews the history of the last 200 years to the modern SynCardia temporary CardioWest Total Artificial Heart.

Currently, the treatments available for advanced forms of cardiovascular disease have been either medical, surgical, or ultimately heart transplantation. Although medical treatment may alleviate some symptoms and improve the patient’s basic quality of life, the overall prognosis remains poor, necessitating a more invasive approach employing techniques of revascularization or valve replacement. Unfortunately, such treatments do not prevent progression of the underlying disease process, making heart transplantation or the implantation of an artificial heart the more desirable option. Although the implantation of a human donor heart might appear to be the solution to all forms of cardiovascular disease, there are many problems, the most obvious being a lack of donor hearts and autorejection, followed by patient selection and cost-effectiveness. There is also the ‘life expectancy’ of the donor heart to be considered. Ten years is the average and 20 is the best-case scenario, so it is an unpromising prospect for those younger than 40 years. Another factor to be taken into account is the necessity for lifelong expensive medical support therapy. Such considerations have been the catalyst for the research and work of bioengineers and physicians in the development of mechanical circulatory support systems. Ultimately leading to the design and manufacture of viable total artificial hearts (TAHs) for implantation into the human body, either as bridging devices until the transplant of a donor heart or as a permanent support for the failing organ.

The road to achieving a truly viable artificial heart has been a long and arduous one, and in the early decades of the twentieth century, any open-heart surgery caused much anxiety and was virtually ‘off-limits.’ As early as 1812, the French physiologist Julien-Jean-Cesar LeGallois (1770–1814) had the idea of supporting the failing heart with either a temporary or more permanent device described in his work ‘Experience sur la principe de la vie’. Paris, 1812—LeGallois was the first to investigate the vascular system, artificial respiration, oxygenation, and preservation of blood.

One of the greatest problems in cardiovascular surgery was to develop a practical means of reconstructing arteries. A surgeon from Lyons, Alexis Carrel (1873–1948), having studied the art of the lacemaker, demonstrated ‘that a piece of the aorta wall could be replaced with a fragment of another artery or vein’ and he ‘developed effective ways of sewing vessels together’. Carrel’s work on anastomosis would lay the foundation for the development of transplant surgery and he personally carried out many animal experiments in 1902.

The next important development came with the research and construction of a machine that could bypass the heart and lung circulation so allowing open-heart surgery. In 1931, John Heysham Gibbon (1903–1973) while working at The Massachusetts General Hospital became obsessed with the idea of a device which would allow for the withdrawal of venous blood for oxygenation and elimination of carbon dioxide, then return to the patient. He persuaded his Director of Surgery to allow him a further year for research and development of a pump. By the early 1950s, Denis Graham Melrose and colleagues in the UK had further developed the heart–lung machine and also employed elective cardiac arrest when carrying out open-heart surgery.1 Further developments and refinements of the heart–lung machines continued during the next decade allowing for many new cardiac interventions including coronary artery bypasses, valve repairs, heart transplantations, and the implantation of TAHs.

In February of 2009, Willem Kolff, inventor of the first artificial kidney and heart machines, died at the age of 97. Dr Willem J. Kolff, a Dutch physician who invented the first artificial kidney during World War II, firmly believed that it was possible for biomedical engineers to build a variety of artificial organs to maintain human life; when it came to hearts his mantra was ‘If a man can grow a heart he can build one’.2 Dr Kolff emigrated to the USA in 1950 where he first joined the Cleveland Clinic Foundation, then in 1967 he moved to the University of Utah to lead the division of artificial organs. It was here that Kolff hired Robert Koffler Jarvik (1946–) physician and biomedical engineer to assist in the development of the artificial heart which he, Kolff, had been working on for some 15 years. Jarvik was able to solve many of the problems associated with these man-made organs. The aim of the artificial heart programme at Utah was to re-create the two lower ventricles. Creating a suitable power source for the pump to be inside the body was one of the major problems in the project. Kolff had tried to create an electrical and then a nuclear power source but with the failure of both such ideas he concentrated on a pump powered with compressed air from an external machine with tubes connecting it to the artificial heart. This meant that the patient would need to be permanently attached to a machine.

When Jarvik joined the institute, he started working on the ‘Kwann-Gett heart’ which had been designed by Clifford Kwann-Gett, a member of Kolff’s team in 1971. The pumping element was supplied via a rubber diaphragm which unfortunately caused blood clotting on its surface. Jarvik worked to improve the device resulting in the ‘Jarvik-3’, and by the mid-1970s, he was working on a version made of aluminium and plastic to replace the ventricles to be attached to the atria. This device known as the ‘Jarvik-7’ was implanted into 61-year-old Barney Clark, a terminally ill retired dentist who was suffering from cardiomyopathy. Post-operatively, Clark suffered disabling brain seizures and died approximately 4 months later of multiple organ failure, albeit, that the artificial heart was still functioning. In the following years, a number of modified Jarvik hearts were developed but none of the recipients lived >620 days. The Jarvik-7 later known as the CardioWest TAH, however, was more frequently and beneficially used as a bridging device for patients awaiting a donor transplant. In the mid-1980s, the clinical application of the Jarvik and other pneumatic hearts provided major news items.

On 29 August 1985, Dr Jack Copeland at the University of Arizona became the first surgeon to use the Jarvik-7 artificial heart as a bridge-to-transplant. On 8 September 1985, his patient, Michael Drummond, received a matching donor heart. News conference, from left to right: Richard Smith, Dr Mark Levinson, Dr Robert Jarvik, Michael Drummond, and Dr Jack Copeland.

However, such devices were associated with a high incidence of thrombo-embolism.

The impracticality of permanent pneumatic artificial hearts became all too evident with such problems as the two large tubes across the chest, the bulky power unit, the alarms plus backups, all requiring the patient to be attached to a large and very heavy power console. The benefit of such results if any was the stimulus provided to establish funding to develop an artificial electric heart.

More than a decade ago, now the development of such devices really took off. Important factors such as the need for the recipient to have free mobility already had established role models such as heart valves, pacemakers, implantable defibrillators, and cardiac transplants setting the standard. The ideal design for an implantable heart would allow all components of the electric model, including power supply, to be implanted within the chest.

References

SynCardia Senior Clinical Support Specialist Steve Langford holds the modern 70cc SynCardia temporary CardioWest™ Total Artificial Heart in right hand, and the older 100cc Jarvik-7 artificial heart in left.

Unfortunately, although we may feel that the TAH can solve all problems related to the morbidity from cardiovascular disease, these amazing devices still carry their own risks associated with serious and often fatal complications. These include severe post-operative bleeding, infection, and thrombo-embolism. Progress in such sensitive and complex areas of medicine is never easy and one might well reflect on avoidance of the problem rather than healing responses to be the most beneficial solution.

Recently, the reported case of a 16-year-old girl who survived 10 years with an implanted ‘piggybacked’ donor organ has raised huge interest and optimism since the girl’s own heart recovered during the prolonged period when it ‘rested’ while her life was maintained thanks to the donor heart grafted on to her own. Unfortunately, after 10 years of immunosuppressants, the young patient developed a rare cancer and the donor heart had to be removed. Amazingly, during the rest period, the girl’s own heart appears to have completely recovered allowing her now to enjoy a normal teenage life. The renowned heart surgeon Sir Magdi Yacoub of the London Harefield Hospital described the recovery of the heart as ‘just like magic’ and felt that it is ‘going to be very fundamental in helping people in the future’.3
Sleep deprivation in doctors: it is an emotive issue and everyone has an opinion. Doctors want to be available to help their patients and also to train the next generation of doctors, but some argue that they are putting patients and themselves at risk for errors and accidents.

When the USA went from unregulated duty hours where residents often worked 100 h a week to regulated duty hours in 2003—the American Graduate Education Council (ACGME) imposed an 80 h a week limit—the assumption was that it would harm patients because of the increased number of handovers. But there is no evidence that these concerns have come to fruition.

What is known is that when doctors work shifts that exceed 16 h, like anyone else, they enter a zone where they are awake at a time when the brain is trying to go to sleep. Lapses of a few seconds may start to occur, which are particularly dangerous for certain activities like driving. Research evidence shows that crash rate risks are quite high, particularly when doctors go home in the morning or during the daytime after being awake all night (Table 1).

A study in the medical intensive care unit and coronary care unit of Brigham and Women’s Hospital in Boston showed that interns make substantially more serious medical errors when they work frequent shifts of ≥24 h, than when they work shorter shifts (Table 2). Interns’ traditional work schedules—which averaged 77–81 h, including up to 34 continuous hours—were compared with an intervention schedule that eliminated shifts of ≥24 h and reduced hours to 63 per week.

The problem with cutting back hours is that it does not guarantee that doctors will get more sleep. Doctors can work long hours and get plenty of sleep; equally they can work shorter hours and get inadequate sleep.

‘Regulating work hours is to some extent a crude way of trying to regulate sleep’, says David F. Dinges. ‘It’s the sleep that matters, that we know unequivocally’.

At the same time, the complete spectrum of factors that contribute to human errors harming patients in hospital is unknown. Fatigue is one component, but it is not the only component.

Worldwide, governments and industry are looking for ways to predict the effect of sleep deprivation more reliably. The problem is that regulations simply stipulate the number of hours that can be worked, on the assumption that people will be less able to function as time goes by.

It means that most work rules do not reflect the biology of sleep, which involves two interacting processes. First, how much sleep people get and the quality of that sleep linearly determines their wakefulness within and across days.

Second is the circadian clock, which interacts with sleep drive and makes it easier to stay awake at sometimes of the day than others. Circadian modulation dictates that if a person stays awake for 40 h from the time they get up in the morning, their greatest period of sleepiness will be at 24 h, not 40 h.

The biology of these processes and their effects on behaviour are so well known that a mathematical model of a circadian oscillator and a quasi-linear process for the sleep drive can be

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**Table 1** Risk of motor vehicle crashes and near-miss incidents after extended shifts*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Extended work shifts (≥24 h)</th>
<th>Nonextended work shifts (&lt;24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crashes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. reported</td>
<td>58</td>
<td>73</td>
</tr>
<tr>
<td>No. of commutes</td>
<td>54 121</td>
<td>180 289</td>
</tr>
<tr>
<td>Rate (per 1000 commutes)</td>
<td>1.07</td>
<td>0.40</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.3 (1.6–3.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Near-miss incidents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. reported</td>
<td>1 971</td>
<td>1 156</td>
</tr>
<tr>
<td>No. of commutes</td>
<td>54 121</td>
<td>180 289</td>
</tr>
<tr>
<td>Rate (per 1000 commutes)</td>
<td>36.42</td>
<td>6.41</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>5.9 (5.4–6.3)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* A within-person case-crossover analysis was used to assess the risks of motor vehicle crashes and near-miss incidents among interns during commutes after extended shifts as compared with nonextended shifts. A two-by-two table was constructed for each intern who reported either a crash or a near-miss incident, consisting of the number of crashes or near-miss incidents after an extended shift, the number of crashes or near-miss incidents after a nonextended shift, the number of extended shifts that did not precede a crash or a near-miss incident, and the number of nonextended shifts that did not precede a crash or a near-miss incident. CI denotes confidence interval.

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Increasingly used to predict, with accuracy, when people will make mistakes.

In 2007, at the request of the US Congress, the Institute of Medicine (IOM) charged the Committee on Optimizing Graduate Medical Trainee (Resident) Hours and Work Schedules to Improve Patient Safety, to evaluate the evidence. The committee’s goal was to recommend ways to improve safety during training, while at the same time ensuring that training was adequate to ensure long-term patient safety after trainees began working on their own.

After looking at all the data, the committee concluded that cutting back hours—which are needed for training—was not the optimum solution. The problem was that residents were not getting enough sleep.

The hours issue is not ignored in the report—there are some limitations of hours, with no averaging of long duty periods—but the issue of sleep is also addressed. For on-call periods of 30 h, the IOM report recommends that after 16 h awake doctors be allowed to sleep in the hospital for up to 5 h, and then complete their rounds the next day and go home.1

But it is not just hours and sleep deprivation that are important, and the committee’s recommendations consider residents’ ability to recover and function at their best. That encompasses a number of issues: Is there adequate supervision of residents by senior physicians? Is the resident workload too much? Do the residents have time to reflect on their clinical experiences so that learning is optimized? Are there training standards as to how proficient a resident needs to be over time?

Are handovers of patients from one physician to another being done effectively, and are there better ways to do them to improve safety for patients? Is there a culture of safety and enhanced teamwork so that everyone involved with the patient is concerned about human error and the patient’s safety? Is there flexibility in scheduling so that the training needs of specialties can be met?

Prof. Dinges, who was on the committee, says: ‘There are definitely things that can be done [regarding sleep deprivation], but the committee felt that you probably won’t have any serious effect on improving patient safety without those other factors also involved’. Europe has a longer history of regulating work hours than the USA, and now has the European Working Time Directive. But Prof. Dinges points out: ‘The problem here is what people say is being done and what is really being done, can be two different things in Europe. There are political statements about “we have this all under control because we have an EU Directive”, then when you drill deeper you may find [that] a lot of physicians opt out of the directive’.

Many doctors recognize that they can make mistakes—or are at risk of making mistakes—when they are tired. Senior doctors will not want to be regulated, but they do want to understand when they are most vulnerable and how they can develop personal strategies to manage their own fatigue.

That needs to include the recognition that doctors’ own sense of how alert or tired they are may not match their actual ability. ‘Particularly with chronic sleep loss, we have repeatedly found that people start to tell you they’ve adapted to it when they’re actually still developing increasingly higher rates of error’, explains Prof. Dinges.

Doctors need to look out for personal behaviours that suggest that there is something wrong, such as lapses of attention or their head falling over for a brief second in the office or in the car.

The major focus in the USA and other countries, including Canada and Australia, is on fatigue management. That includes when to sleep, when to take naps, how to use caffeine, and how to identify who is more vulnerable to the effects of sleep deprivation.

The trick is that in addition to mitigating the effects of tiredness, doctors have to learn to get sleep when they are off duty. It is one of the reasons why the IOM report recommends that moonlighting, outside of the main training job, should not be permitted. Prof. Dinges admits that the idea may not be popular because it is a way for doctors to supplement their income, but he adds: ‘If people don’t sleep, if they go and work a second job because they’re underpaid, then you haven’t solved anything’.

Views for and against regulation are equally intense, but the hard evidence for both sides’ claims it is not as extensive as one would like. Larger studies are needed in order to understand what other

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### Table 2  Incidence of serious medical errors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Traditional schedule</th>
<th>Intervention schedule</th>
<th>( P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious medical errors made by interns</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious medical errors</td>
<td>176 (136.0)</td>
<td>91 (100.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preventable adverse events</td>
<td>27 (20.9)</td>
<td>15 (16.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>Intercepted serious errors</td>
<td>91 (70.3)</td>
<td>50 (55.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonintercepted serious errors</td>
<td>58 (44.8)</td>
<td>26 (28.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Types of serious medical errors made by interns</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>129 (99.7)</td>
<td>75 (82.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Procedural</td>
<td>11 (8.5)</td>
<td>6 (6.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>24 (18.6)</td>
<td>3 (3.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Other</td>
<td>12 (9.3)</td>
<td>7 (7.7)</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>All serious medical errors, unit-wide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious medical errors</td>
<td>250 (193.2)</td>
<td>144 (158.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preventable adverse events</td>
<td>50 (38.6)</td>
<td>35 (38.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>Intercepted serious errors</td>
<td>123 (95.1)</td>
<td>63 (69.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonintercepted serious errors</td>
<td>77 (59.5)</td>
<td>46 (50.6)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Types of serious medical errors, unit-wide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>175 (135.2)</td>
<td>105 (115.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Procedural</td>
<td>18 (13.9)</td>
<td>11 (12.1)</td>
<td>0.48</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>28 (21.6)</td>
<td>10 (11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>29 (22.4)</td>
<td>18 (19.8)</td>
<td>0.45</td>
</tr>
</tbody>
</table>
factors contribute to errors, what the risks of certain duty hours are, and what other factors limit residents’ sleep. Even less is known about fully trained doctors. Studies on the benefits of fatigue management systems over time are also needed.

‘The real problem is that no one wants to take any time or invest any money to get an evidence based approach to the problem’, says Prof. Dinges. ‘Everyone wants to argue about regulation’.

In such a heavily politicized topic, it can lead to bad decisions if people make guesses about what should be done based on their own political agendas.

The challenge is how to manage—in healthcare systems that process millions of patients and train the next generation of doctors, all in a 24/7 environment—the fatigue that can pose risks to both doctors and patients.

It is crying out for an evidence-based approach, which means scientific work must be done. Prof. Dinges concludes: ‘We have plenty of opinion, we need some evidence’.

Jennifer Taylor, MPhil

References