Vincent’s Fall Sense

This month’s 2014 September ISHLT Links Newsletter provides a spotlight on 36 Hours in Nice. As we anticipate the Mediterranean breeze of next year, Jim Coons from the University of Pittsburgh Medical Center gives us a Breath of Fresh Air summarizing the pharmacotherapeutic advances in treating pulmonary arterial hypertension and their correlation with reduced morbidity and mortality in the sufferers of pulmonary hypertension. Also, Christina Doligalski of Tampa General Hospital enlightens us on the Link between PDE5-Inhibitors and Melanoma and how to risk assess such a complex population who would rather not be kept in the dark. Amresh Raina from Allegheny General Hospital further moves us Into the Digital Age with The Promise of Implantable Hemodynamic Monitoring to manage patients with pulmonary arterial hypertension while Veronica Franco updates us on What’s New in Pulmonary Hypertension.

Also included are several ISHLT announcements: the ISHLT Newest Grant Award Winners, the Transplant Registry Early Career Award, and the ISHLT’s encouragement to persuade, coerce, or compel all of you to GO! Write! Win! with the Links Travel Awards.

And to conclude this issue, check out a taste of contention between Rousseau and Voltaire with thoughts worth thinking, and my more in-depth analysis in the Editor’s Corner: Voltaire and the Man Who Knew Too Much, Que Sera, Sera. By the way, your Editor really knows nothing, therefore he writes too much.

Vincent Valentine, MD
Links Editor-in-Chief

IN THE SPOTLIGHT: 36 Hours in Nice from the New York Times

On the southeast coast of France, Nice welcomes travelers with alluring restaurants, a broad beach, sherbet-hued buildings and gay-friendly night life. Packing year-round sun, the Mediterranean Sea, belle époque and Art Deco architecture, Nice attracts visitors with the bonuses of an atmospheric old quarter, an evolving restaurant scene, the Riviera's best museums and some high-profile public works. A city for all budgets, Nice buzzes with an energy and diversity that often surpasses its coastal rivals.

"It is often said that in Nice, we are always on vacation. Which indeed, isn't wrong."

"You should be thinking to come to Nice one time in your life because it's probably one of the most beautiful cities in the world. Honestly, you cannot find a place like Nice elsewhere."

See more in 36 Hours in Nice ➔
Pharmacotherapeutic advances in the treatment of pulmonary arterial hypertension (PAH) have coincided with reductions in overall morbidity and mortality for this progressive, fatal disease [1,2]. Despite these improvements, PAH, in the modern management era, is still associated with a significant clinical burden for patients in the form of advanced symptoms, poor quality of life, and suboptimal outcomes [3]. The mainstays of treatment encompass prostacyclins, endothelin receptor antagonists (ERA) and phosphodiesterase-type 5 (PDE-5) inhibitors. The year 2013, however, was particularly notable in the PAH field as three new medications gained regulatory approval: riociguat (Adempas®), macitentan (Opsumit®), and oral treprostinil (Orenitram®) [4-6]. Riociguat also became the first approved medication to treat select patients with chronic thromboembolic PH (CTEPH). In parallel, new international evidence-based treatment guidelines for PH were published and integrate new data with riociguat and macitentan [7]. Consequently, the focus of this article will be on these therapies. A focused review of oral treprostinil was previously published in the March 2014 issue of the Links by Dr. Veronica Franco.

Riociguat is the first approved medication in a novel therapeutic class known as soluble guanylate cyclase (sGC) stimulators. sGC is the molecular target for nitric oxide (NO) and is responsible for the enzymatic production of cyclic guanosine monophosphate (cGMP). Riociguat acts by sensitizing sGC in the presence of NO, but is also effective when NO is depleted. Ultimately, the principal therapeutic effect is vasodilation but there are also antithrombotic, antiproliferative, and anti-fibrotic effects that are mediated [8].

Riociguat was evaluated in two landmark, international, placebo-controlled trials of different patient populations. The PATENT-1 trial enrolled 443 patients with World Health Organization (WHO) Group I PAH (61% idiopathic, 25% associated with connective tissue disease [CTD]) and primarily WHO functional class (FC) II and III symptoms [9]. 44% of patients were on background treatment with an ERA, whereas only 6% of patients were on a prostanoid (mostly inhaled iloprost). The primary efficacy analysis revealed a 36 meter increase in the 6MWD at 12 weeks with riociguat (target dose of 2.5 mg PO tid) vs. placebo (p<0.001) from a baseline of 363 meters. Other secondary endpoints demonstrated improvements in hemodynamics (HD), WHO FC, and time to clinical worsening [9]. The CHEST-1 trial enrolled 261 patients with inoperable CTEPH [72%] or persistent or recurrent PH after pulmonary endarterectomy (PEA) [28%]. The majority of patients were in WHO FC III (64%). Overall, riociguat was associated with a 46 m increase in 6MWD at 16 weeks with riociguat (target dose of 2.5 mg PO tid) vs. placebo (p<0.001) from a baseline of 348 meters. Significant improvements were also found in HD and WHO FC [10].
Current treatment guidelines for PAH recommend riociguat as a potential alternative to a PDE-5 inhibitor for patients with primarily WHO FC II or III symptoms [7]. For inoperable CTEPH and residual disease despite PEA, riociguat would be recommended as a first-line therapy based upon the positive findings from the CHEST-1 trial [11].

Macitentan is the most recently approved ERA which exhibits dual inhibition of endothelin-A and –B receptors. It is a synthetic derivative of bosentan characterized by increased tissue penetration and sustained receptor binding [12,13]. Like other ERA’s, macitentan exerts vasodilatory, antiproliferative, and anti-fibrotic effects [7,12].

Macitentan was evaluated in the landmark, international, SERAPHIN trial which was an outcomes-driven study of 742 patients with Group I PAH (55% idiopathic, 30% associated with CTD) and primarily FC II and III symptoms [14]. Approximately 60% of patients were on background PDE-5 inhibitor therapy, but only 5% were receiving an inhaled or oral prostacyclin. Patients were randomized to 3 or 10 mg macitentan once daily or placebo and followed for approximately 100 weeks. The primary composite endpoint was the time to first event related to PAH (worsening of PAH [defined as decrease in 6MWD by ≥ 15% from baseline, worsening of symptoms, and need for additional treatment], initiation of treatment with IV or SC prostanoids, lung transplantation, or atrial septostomy) or all-cause death. The composite endpoint was significantly lowered with macitentan (3 mg; p = 0.01) and (10 mg; p < 0.001) vs. placebo. The benefit of macitentan was driven mainly by a reduction in worsening of PAH and fewer PAH-related hospitalizations [14].

The current PAH guidelines recommend macitentan for patients with primarily WHO FC II or III symptoms [7]. Macitentan may be preferable to bosentan based on the lower risk of transaminitis (incidence > 3 times upper limit of normal with macitentan not different vs. placebo) and lack of requirement for monthly liver function monitoring.

<table>
<thead>
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<th>Adverse Events</th>
<th>Monitoring</th>
<th>Risk Management Program</th>
<th>Drug Interactions</th>
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<tbody>
<tr>
<td><strong>Riociguat</strong></td>
<td>Headache, dizziness, dyspepsia, reflux,</td>
<td>-Baseline &amp; monthly pregnancy tests</td>
<td>Yes</td>
<td>-Strong CYP 3A4 inhibitors and p-</td>
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<td>nausea, vomiting, diarrhea, anemia,</td>
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<td>glycoprotein inhibitors</td>
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<td>hypotension, † teratogenicity</td>
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<tr>
<td><strong>Macitentan</strong></td>
<td>Nasopharyngitis, headache, anemia,</td>
<td>-Baseline liver function tests</td>
<td>Yes</td>
<td>-PDE-5 inhibitors</td>
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Patients at risk for hypotension or receiving interacting medications (see table) should start at 0.5 mg PO tid. Dosing titrations should not occur more often than every 2 weeks and BP should be monitored during these intervals [4].

Hemoglobin drop to ≤ 8 g/dL was 4.3% in the 10 mg group [14]

In summary, ongoing medical advances in PAH and CTEPH have been commensurate with the availability of new medications, formulations, and identification of novel therapeutic targets. Each of these therapies offers patients and clinicians the potential for improved outcomes in managing these complex diseases.

Disclosure statement: The author has no conflicts of interest to disclose.

References:

Shining a Light on the Link between PDE5-Inhibitors and Melanoma

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Breaking News
Practicing in Florida, I read with great interest the recent study potentially linking sildenafil and melanoma [1]. The evening news was awash with cautionary warnings for middle-aged men, while simultaneously ruining many 24 hour news channels’ daytime advertising base.

Early Research
The first correlation between PDE5A and melanoma was reported in 2008 [2,3], following several years of groundbreaking research in which the cellular pathways of melanoma were being elucidated [4-7]. This research identified two key regulatory melanoma pathways, both of which are effected by PDE5A expression. The most significant pre-clinical finding came in 2011, when Arozarena and colleagues [8] investigated the physiologic relevance of PDE5A to melanoma, and were able to find that PDE5A inhibition produced increased melanoma invasion, while PDE5A stimulation produced stable or decreased invasive potential. These findings led to the question: Is there a clinically-significant link between melanoma and sildenafil use? [9]

The Latest Data
In Li and colleagues’ analysis, a cohort was followed from 2000 to 2010. At baseline, men in the United States reported their use, ever or current, of sildenafil (the only commercially available PDE5A inhibitor at the time) for erectile dysfunction. Additional information including other known risk factors for melanoma was also assessed. Participants then reported diagnoses of melanoma, squamous cell cancers (SCC), basal cell cancers (BCC), and other cancers on biennial surveys. Self-reported cancers were only included if they were pathologically confirmed via review of their medical record. Risk was then analyzed by assessing melanoma cases in those who were using sildenafil in 2000 compared to those who were not in 2000; those men who developed erectile dysfunction (ED) and began use of PDE5A inhibitors after 2000 were not identified and were therefore included in the “no sildenafil” group.

Of the 25,848 participants included in the analysis, there were 142 cases of melanoma: 128/193,935 (0.07%) in the “no sildenafil” arm, and 14/10,935 (0.13%) in the “sildenafil” arm. The average patient was, as expected, a 65 year old white male, with 68% having “burn or blistering skin reaction to the sun”. After adjusting for multiple factors (including known risk factors for melanoma), the hazard ratio for incident of melanoma associated with use of sildenafil was 1.84 (1.04-2.33). This increased risk association was not seen with SCC (HR: 0.84 [0.59-1.20]) or BCC (HR: 1.08 [0.93-1.25]).
What the author's did not explicitly state, however, was that the absolute risk of development of melanoma in men receiving sildenafil was 0.128%, or 1 cancer case per 781 person-years. Additional limitations of this study included its lack of melanoma outcomes data (survival, treatment, etc), lack of dosing information for sildenafil, and potential for underestimation of risk given that new use of sildenafil was not captured in the “no sildenafil” group after 2000.

**The Dilemma**

PDE5A inhibitors are mainstays in the therapy of pulmonary arterial hypertension and PAH from left heart disease (PH-LHD). These recent data are especially concerning given the cumulative and persistent exposure to PDE5 inhibition in PAH/PH-LHD in the patients we serve compared with occasional use seen in ED. Unfortunately, alternative therapies for PAH or PH-LHD are not innocuous and carry much more concrete potential adverse events, inconvenient dosing, and extensive costs.

Additionally, early research pointed to an increased risk of melanoma's *invasiveness*, not in melanoma *development*. This point was raised by Li and colleagues, in which they suggested that perhaps those who received sildenafil had acceleration in development of melanoma through PDE5 inhibition; essentially that PDE5A inhibitors "may promote invasion of primary tumors". However, it is important to remember that retrospective cohorts can only suggest an association, not prove cause and effect relationships. Perhaps other pathways are responsible for the increased risk seen with sildenafil use, such as PDE5A inhibitor's promotion of melanin synthesis. [10-11]

**The Solution**

Unfortunately, a definitive risk assessment in our patient population is unlikely to occur given the incredibly low absolute risk and large population that would be needed to properly assess this risk. In a commentary to Li’s analysis,12 the point is made that the only known modifiable cause of melanoma is exposure to UV radiation. In patient’s presenting with PAH or PH-LHD in which sildenafil (or any PDE5-inhibitor therapy) is being considered, a careful assessment of past UV exposure, frequent follow up with a dermatologist, and education on self-screening should be considered in light of available data until a more definitive cause/effect relationship can be determined.

Disclosure statement: the author has no conflicts of interest to disclose.

References:


Into The Digital Age: The Promise of Implantable Hemodynamic Monitoring in the Management of Pulmonary Arterial Hypertension

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In May 2014, the United States Food and Drug Administration (FDA) approved the first implantable hemodynamic monitor (IHM) for the treatment and monitoring of New York Heart Association (NYHA) functional class III heart failure (HF) [1]. The CARDIOMEMs device (St. Jude Medical, St. Paul, MN), is a wireless sensor placed in a distal branch of the pulmonary artery during right heart catheterization (RHC), and transmits measured pulmonary artery (PA) systolic, diastolic and mean pressures via an external console to a secure website, accessed by a patient’s physician (Figure 1). This sensor also has the potential for measurement of cardiac output, but this algorithm remains to be validated.

Though this device was approved based on reduction of HF hospitalizations in patients with left heart failure [2], the hemodynamic information it provides could be easily applicable to the management of patients with pulmonary arterial hypertension (PAH).

Within two weeks of the FDA approval, one of our tech-savvy PAH patients posed exactly this question. He pulled out a picture of the CARDIOMEMs device printed from the internet during an office visit and asked whether he might be a candidate for this new technology, especially if he could access his PA pressures at home, and if the device could replace having future ‘archaic’ right heart catheterizations.

For better or worse, many PAH patients remain focused on PA pressures, as these are perhaps the easiest component of the hemodynamic assessment for a lay-person to understand and track, and, at least in the sentinel National Institutes of Health Registry, mean PA pressure was a main component associated with survival [3]. Though other hemodynamic variables, such as right atrial pressure and pulmonary vascular resistance (PVR), have subsequently been found to better predict outcomes in PAH patients [4,5], ongoing hemodynamic assessment may be useful in the management of PAH.

Indeed, there are several clinical scenarios where IHM data might be used to supplement traditional hemodynamic assessment with RHC. Perhaps the biggest advantage of IHM monitoring is that it provides ongoing and frequent assessment of a patient’s hemodynamics in the outpatient setting. It can also give a more complete understanding of a patient’s overall hemodynamics versus RHC which is performed intermittently at best, and under somewhat artificial conditions, typically supine and at rest. A recent small study of IHM monitoring in PAH patients showed that there was a more dramatic variation in PA pressures with daily activities versus with six minute
walk testing, or even with cardiopulmonary exercise testing [6]. This becomes particularly relevant to the assessment of patients who have predominantly exercise-induced PAH symptoms and those who have borderline PAH (mean PA pressures 20-25 mm Hg) on resting RHC.

Another potential advantage with IHM monitoring in PAH might be in the prevention of hospitalization for right heart failure. In patients with left heart failure, a rise in PA pressures often occurs several days prior to the onset of new or worsening symptoms [7], allowing a window for medical intervention and prevention of hospitalization. The same logic could be applied to patients with PAH. Of course, PA pressures can rise due to an increase in PVR or an increase in cardiac output, but current IHM systems have the potential for estimating cardiac output to help discriminate between these possibilities. Moreover, in patients with PAH, wedge pressure is typically normal and assuming a normal wedge pressure, the IHM system could then provide an ongoing assessment of PVR.

Knowledge of PA pressure and PVR might also be helpful to rapidly gauge the efficacy of PAH specific therapy. For example, when starting oral agents, PAH clinicians initiate a therapy and then wait weeks to months before reassessing a patient’s symptoms, functional status, right ventricular imaging, and potentially invasive hemodynamics. In two small studies with IHM monitoring in PAH patients, IHM data informed changes in medical therapy. Among two PAH patients transitioned from iloprost to bosentan, IHM data allowed clinicians to see the acute efficacy of bosentan over a week of therapy, allowing for successful discontinuation of iloprost [8]. In a multi-center study of 24 patients with PAH who had IHM implant prior to planned change in PAH therapy, the IHM data identified 13/15 patients who improved their six minute walk distance greater than 30 meters [9]. IHM data might also aid the titration of patients with intravenous prostanoid therapy, allowing the PH clinician to tailor a ‘goal’ dose individualized to the patient and their response to the particular prostanoid agent.

Finally, PAH patients may be able to enjoy a greater degree of autonomy and a reduction in the number of visits to the tertiary care center with the use of IHM monitoring. Many PAH patients live several hours away from tertiary PAH referral centers and participate in shared care with their local physicians. Through remote monitoring with an IHM, local physicians and those at referral centers may be able to facilitate shared care, reducing the need for long trips to a referral center and for invasive procedures, such as RHC with its associated risk and discomfort.

So is the use of IHM systems in PAH ready for ‘prime time’? Though the advent of this new technology is certainly exciting for the heart failure and PH community, patients and clinicians should be aware that the clinical experience to date with IHM systems in PAH is very small, and has been limited to small cases series and small multicenter studies, such that efficacy data remains lacking. Similarly, relatively little safety data exists with IHM devices in PAH patients, though the data that is available is positive. In the CHAMPION trial of the CardioMEMS IHM in 550 patients with left sided congestive heart failure, 48 (9.2%) patients had PH with a significant component of pulmonary vascular remodeling, a clinical phenotype similar to PAH. In this patient subset, there was only a single device/system related complication, which was actually associated with the
implantation RHC [2]. The device/system related adverse event rate in this subgroup was not statistically different than the established rate of adverse events for a RHC in PH [10].

With the combination of so many possible benefits of IHM monitoring in PAH combined with the relative paucity of efficacy and safety data in this patient population, this may be an ideal time to consider a larger clinical trial of IHM monitoring in PAH patients and to consider use of IHM data as surrogate endpoint in future PAH therapeutic clinical trials.

Figure 1: CardioMEMS Heart Failure System Including Pressure Sensor, External Measurement Unit and Sample Pulmonary Artery Pressure Measurement Screen
Disclosure statement: Dr. Raina has received consulting and speaking fees from United Therapeutics Corporation.

References:
What’s New in Pulmonary Hypertension?

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Preparations for the 2015 ISHLT meeting are underway and it promises to be a great collection of symposia in the beautiful city of Nice. The world of pulmonary hypertension is also full of exciting news. Today, PH specialists have many more treatment options than they did a decade ago and three new medications have been approved as of 2013 [1,2]. Additional studies on these newer medications were presented at the American Thoracic Society (ATS) meeting in May 2014.

Data from the SERAPHIN trial was presented by Dr. Mehta; 10 mg daily of Macitentan, an endothelin receptor antagonist, significantly reduced all-cause hospitalizations in PAH patients compared to placebo. SERAPHIN [1] was an event driven study where double-blinded therapy was continued until patients either experienced a primary endpoint (morbidity or mortality) event or until the end of study. Of the 250 patients in the placebo group, and the 242 patients in the macitentan 10 mg group, 117 (47%) and 90 (37%) were hospitalized at least once, experiencing 171 and 135 hospitalizations over a median treatment duration of 85 and 104 weeks, respectively. The risk of hospitalization for causes unrelated to PAH was similar between patients on placebo and those treated with macitentan 10 mg (HR 0.890; 95% CI 0.616–1.285; p=0.5347). Compared with the placebo, the risk of being hospitalized for any cause was significantly reduced by 32% with macitentan 10 mg (HR 0.677; 95% CI 0.514–0.891; p=0.0051) (Figure). The annual rate of all-cause hospitalization was reduced by 33% with macitentan 10 mg compared with placebo (27.7 vs 41.5 hospitalizations per 100 patient-years, respectively; p=0.0005).

There is a paradigm change in clinical trials in PAH, calling for newer and improved trial design in this orphan disease [3]. The PH community will continue to look for novel therapies that will not only improve functional capacity, but also morbidity and mortality. The SERAPHIN trial studied important aspects in the care of PAH patients, such as hospitalizations. Current developments in PAH therapeutics and better trial design with robust clinical outcomes will certainly continue to improve the state of the disease.
Another interesting study was presented at ATS by Dr. White. It discussed the safety and tolerability of transitioning from parental to oral treprostinil [2] in patients with PAH. This was a preliminary report of an ongoing, open-label, multi-center study for subjects with well-compensated PAH being managed with parental treprostinil (25-150 ng/kg/min) plus an oral PAH-specific therapy. Participants were included if they had WHO functional class I/II symptoms and cardiac index ≥ 2.2 L/m/m². 27 subjects were enrolled. Baseline demographics included a median age of 50 years (18-80) and median 6MWD of 457 meters (279-641); most patients were idiopathic or heritable PAH (n=19). The median treprostinil dose at baseline was 54 ng/kg/min (25-124.5). Seven patients were receiving ERA & PDE5-I, seventeen PDE5-I, and three ERA therapy. The majority of patients were transitioned to oral treprostinil within 4 days as inpatients. 10 patients were transitioned to oral treprostinil BID and 17 patients to TID dosing. At the end of the transition phase, the median total daily dose of oral treprostinil was 24 mg. Only 9 patients have reached 6 months evaluations by the time this trial was presented. 17 are ongoing, and 1 patient with scleroderma did not tolerate oral treprostinil (after transition) and returned to parenteral treprostinil. Interim data were available on the first 9 patients to reach 6 month follow up. Median 6MWD was 453 meters (354-641) with no worsening of functional class. Pharmacokinetic analyses confirmed that 1 mg TID ~ 5 ng/kg/min in terms of treprostinil exposure (AUC) for a typical 70 kg patient.

This study was small and follow up at 6 months was only available in 9 patients; however, it provides important information to a question in everyone’s mind: are we ready to change stable patients on IV or SQ treprostinil to oral therapy? Interestingly, this was a question many had ~ 10 years ago, when the only available therapy was IV epoprostenol and bosentan was approved. In the current era, we certainly have a significant number of patients only on oral specific PAH therapy. The adequate timing to start parental prostacyclins remains controversial, and many experts in the field advocate for “the earlier the better.” Patients, on the other hand, are excited about not dealing with an intricate system and using a “much simpler pill.” Interestingly, the oral therapeutic alternative is now another prostacyclin. This study shows that stable and very carefully-selected PAH patients can be safely transitioned to oral treprostinil without a significant decline in exercise capacity at least up to 6 months. Yet, the most important question remains: will the long-term efficacy be comparable to parental prostacyclins? Stay tuned!

Other important trials will also be presented at upcoming meetings, such as the European Respiratory Society and American College of Chest Physicians. 1) The AMBITION trial evaluated an upfront combination of Ambrisentan and Tadalafil for patients with PAH. There are several potential advantages of using combination treatment. Using combination therapy may provide additive, and in some cases synergistic, benefit by simultaneously addressing multiple disease pathways. Currently, physicians use a goal-directed approach to combine agents from different classes to target multiple pathologic pathways in an attempt to increase efficacy and optimize outcomes in PAH. If a patient has not reached the goal walk distance, functional class or hemodynamic ideal response, an additional medication is added after 3-6 months. Yet, supporting data for this approach are largely anecdotal and its use remains controversial. AMBITION has been designed to answer this important question; 2) The GRIPHON study evaluated the efficacy of oral selexipag, a prostacyclin IP receptor agonist that is highly selective for the human prostacyclin IP receptor.
Prostacyclin analogs are not selective and activate other prostacyclin receptors. The very selective profile of selexipag causes greater vasodilatory effects than iloprost. Selexipag has a half-life of ~8 hours, making it an attractive candidate for clinical use.

Disclosure statement: The author is a speaker bureau/consultant for Gilead and Bayer, and has received research support from Bayer, Actelion, Gilead and United Therapeutics.

References:
ISHLT New Grant Award Winners Announced

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On behalf of the ISHLT Grants & Awards Committee, we are pleased to announce the winners of the ISHLT/Bayer Pulmonary Hypertension Research Grant Award and the ISHLT/HeartWare Award for Translational Research in Mechanical Circulatory Support. From 20 applications for the ISHLT/Bayer award and 22 applications for the ISHLT/HeartWare award, one winner was selected for each award:

ISHLT/Bayer Pulmonary Hypertension Research Grant Award winner:

Benjamin Freed, MD  
Northwestern University, Chicago, IL, USA  
Director of Research: Sanjiv J. Shah, MD, FAHA, FACC  
Project: "Non-invasive Detection of Right Ventricular Interstitial Fibrosis using MRI in Patients with Pulmonary Hypertension due to Heart Failure with Preserved Ejection Fraction"

ISHLT/HeartWare Award for Translational Research in Mechanical Circulatory Support winner:

Leigh Reardon, MD  
UCLA, Los Angeles, CA, USA  
Director of Research: Jamil Aboulhosn, MD, FACC, FSCAI  
Project: "Mechanical Circulatory Support for the Fontan Circulation"

The ISHLT/Bayer Pulmonary Hypertension Research Grant Award is a two-year award in the amount of $100,000 ($50,000 per year). The purpose of the Award is to further the scientific understanding of Pulmonary Hypertension, with the ultimate aim of improving patient's lives. The Award is designed to support young scientists, doing research in Pulmonary Hypertension at a critical time in their independent research careers. The goal of the study must be to investigate a relevant clinical or translational science question in PH, irrespective of the PH subtype.

The ISHLT/HeartWare Award for Translational Research in Mechanical Circulatory Support is a one-year award in the amount of $65,000. The purpose of the Award is to support research utilizing MCS that would result in an increased understanding of the biologic effects, use
as sole or combined therapy, insights into patient/MCS management, innovative use/application or improved outcomes for the treatment of heart failure. The Award is aimed to support rising stars in the field of mechanical circulatory support at a critical time in their career. The Award recipient will have already established a track record in the field of mechanical circulatory support and will aim to further develop their career in this area. The intent is that the Award will be for a junior faculty position dedicated to a career in the use of MCS as a treatment option for heart failure. It is anticipated that the individual will be clinician or clinician scientist at an active VAD/transplant program with a faculty appointment in either cardiology or cardiac surgery.

The ISHLT would like to thank the following reviewers for their hard work and contribution in helping to select these two outstanding award winners.

**ISHLT/Bayer Reviewers**
Ray Benza, USA (Chair)  
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Mark Slaughter, USA  
Joseph Rogers, USA  
Evgenij Potapov, Germany  
Andreas Zuckermann, Austria

For more information about these and other ISHLT Grants and Awards, please visit our website at [www.ishlt.org/awards](http://www.ishlt.org/awards).

Disclosure statement: the authors have no conflicts of interest to report.
Announcement:
Transplant Registry Early Career Award

Summer greetings from the Junior Faculty and Trainee Council of the ISHLT! As you return from summer holiday/vacation, we wanted to alert you to an exciting opportunity that is available from ISHLT for fellows and junior faculty. The Transplant Registry Early Career Award is given annually to a fellow or junior faculty member to fund a clinical research project that utilizes the ISHLT registry. The deadline for submission will be January 15, 2015, and up to three awards will be funded.

To be eligible to receive the award: 1) the applicant or the research project director must be a member of the ISHLT at the time of application and throughout the period of funding, 2) the applicant must be a fellow or junior faculty (instructor or assistant professor level) at the time of application, and 3) the applicant must not have already received extramural funding for the same time period.

The award is for $5000 (3745 €) over one year. The award also includes statistical support to define study groups and generate a dataset for the analysis. This part of the project is supported by the Registry lead statistician Leah Edwards, Ph.D. The full analysis is then to be performed by the awardee, with statistical support at their institution, or, alternatively, the awardee can request further statistical support from the Registry statistical core. If statistical support beyond the dataset generation is requested from the Registry, a contract will be set up between the applicant’s institution and the Registry, and an appropriate amount of the grant funds will be used to cover the cost of the statistical support. The awardees are strongly encouraged to also involve one of the registry associate directors in data analysis and interpretation.

If you are interested in applying for the award but don’t have a suitable research project director at your institution, the Registry steering committee will assist with finding a suitable project director.

For full details about the award please visit the ISHLT Transplant Registry Early Career Award website where you can also access a sample application to review (with thanks to Dr. Nativi and Dr. Stehlik).

For other questions about the application process, please contact Phyllis Glenn at Phyllis.glenn@ishlt.org.

Sincerely,
the Junior Faculty and Trainee Council
Links Travel Awards: Go! Write! Win!

With the support of W.O. and Joan Leach (Gadsden, Alabama, USA), Mrs. Sue Abramson (Birmingham, Alabama, USA) and Mr. Larry Imhoff (La Place, Louisiana, USA), ISHLT has been able to offer the Leach-Abramson-Imhoff Links Travel Awards to support the growth and development of our future leaders from within our society. From physicians to nurses to other healthcare professionals, anyone motivated enough by investigation, communication, and dissemination of new ideas for the betterment of patients with failing lungs and/or a failing heart should be rewarded for their efforts. Whether writing about conditions such as pulmonary fibrosis, cystic fibrosis, emphysema, pulmonary hypertension, and from ischemic, nonischemic to congenital heart diseases, those who work tirelessly to educate themselves, their patients and their field should not go unnoticed or unmentioned.

Eligibility requirements include:

1. Any healthcare professional including but not limited to nurses, nurse coordinators, social workers, pharmacists, therapists, dietitians and early career physicians are eligible and must be a member of the ISHLT regardless of duration in their career.
2. An imposed restriction on physicians is that they must be in their Early Career—within 7 years of training, Assistant Professor equivalent, or junior faculty level with rare exceptions.
3. Individuals must display some form of research interest, basic, clinical, translational or outcomes investigations or at a minimum display some skill in journalism best exemplified by their contributions to the Links Newsletter engendering fresh and creative ideas.

Each year, winners are selected from a pool of nominees by the ISHLT Links Travel Award Committee (LTAC) which includes: the Links Editor-in-Chief, ISHLT Executive Director, ISHLT President, ISHLT Program Chair, and the Links Managing Editor. Past and present award winners are announced on the Links Newsletter Awards page of our website.

By submitting one (or more!) article(s) for publication in any of the 2014 ISHLT Links Newsletter issues AND meeting the above eligibility requirements, any author can be considered for one of these awards. Please visit Links Schedule & Deadlines for upcoming issue deadlines and content information.

So go! Write! Win! And don’t forget to tell us all about it when you get back, as we do so enjoy hearing from our members!

ISHLT Editorial Staff
Alfred Hitchcock’s suspense thriller, *The Man Who Knew Too Much*, was released and included the Oscar Award winning, “Whatever Will Be, Will Be” (Que Sera, Sera) sung by Doris Day, who starred with James Stewart in 1956, precisely 200 years after Jean-Jacques Rousseau wrote a furious response to Voltaire’s *Poem on the Lisbon Disaster* published in 1756.

The Lisbon earthquake shook Europe on November 1, 1755 and left Lisbon in ruins and seared Voltaire’s and Europe’s consciousness at a time when 18th Century Europe was enlightened; seeing through nature to the God of nature, and through the laws of nature to the wisdom and beneficence of God. In his poem, Voltaire reassessed his Leibnizian optimistic philosophy and theology, seeing evil and suffering as inexplicable given that God is infinitely good, and asserting that suffering humanity requires his love more than God does. The furious response from Jean-Jacques Rousseau accused Voltaire of attacking the Divinity. Voltaire’s influential Poem on the Lisbon Earthquake and his most enduring work more closely associated with the modern mind, *Candide*, transformed Voltaire from a philosophical optimist to a philosophical humanist. He then rejected philosophical optimism and considered it, instead, to be anti-humanistic.

To better understand Leibnizian philosophy, let’s recall Gottfried Wilhem Leibniz of Leipzig, Saxony, Germany 1646 – 1716. A great mathematician and philosopher, he was credited, along with Sir Isaac Newton, with the discovery of calculus. The works of Newton and Leibniz are still evident today in the commonly used calculus notations. Newton introduced the notation \( f \), the derivative of a function \( f(x) \) and Leibniz introduced \( \int \), the elongated S from the Latin word *summa*, for the integral and wrote the derivative of a function, (using the \( d \) used for differentials from the Latin word *differentia*), \( y \) of the variable \( x \) as \( \frac{dy}{dx} \) which remain in use. Unlike Newton, Leibniz saw the tangent as a ratio between ordinates and abscissas from Descartes’ Cartesian coordinates. Leibniz’s reasoning led him to believe that the integral was the sum of the coordinates for infinitesimal intervals in the abscissa, or the sum of an infinite number of rectangles. It became clear that the integral has an inverse relationship with the differential. While Newton avoided infinitesimals, Leibniz made infinitesimals the pillars of his notations and calculus.

Now, recall from the ISHLT June 2014, Volume 6, Issue 2 on *Voltaire, The Enlightenment and the The Wit (WIT)* that it was Madame du Châtelet who introduced Voltaire to Leibnizian philosophy. Initially, Leibnizian philosophy appealed to Voltaire’s sense of God known through nature, which attracted a large and growing number of European thinkers. Philosophical optimism originated from Leibniz’s Essays on Theodicy. Theodicy is that
branch of philosophical theology that deals with the problem of evil. Rationally, Leibniz had no problem thinking in terms of infinity or infinitesimals. Leibniz posits that for everyone who believed in a God who is infinitely wise, infinitely powerful, and infinitely good, he sets this as a mathematic given, or what is known. What then logically follows with absolute and geometric certainty is that God would not create a perfect world because He is the only perfect being; therefore He can only create “the best of all possible worlds.” God has full divine knowledge of how everything fits into the world with no true evil. Leibniz was an optimistic philosopher and concluded, as a matter of logic, that though you may not know the reasons why, God had a necessary and sufficient reason for everything is in this world. If something serves a good purpose, it is not evil. A medicine for a child that tastes horribly or is painful may be good and helpful and therefore is not an evil. Parents know that the medicine or “shot” will make the child better. The child believes it is evil. As the child ages, he learns it is not evil. From this Leibniz argues that God chose everything in the creation as necessary and sufficient and, therefore, good. Nothing that appears evil in the creation is evil. If we possessed God’s knowledge, then we would understand the good of what we might think, from our limited perspective, to be evil. As Alexander Pope put it from his Essay on Man, “Whatever is, is right.” Or to restate it, whatever will be, will be. This is precisely what troubled Voltaire.

Voltaire was always skeptical about philosophical optimism. Despite best efforts to support it, probably out of his love for Madame du Châtelet, The 1750’s saw his vehement rejection of Leibnizian optimism. It started with the tragic death of Madame du Chatelet. Devastated by her death and disgraced by the French court (he was unwanted in Paris, he accepted an invitation to live at the court of King Frederick II of Prussia. There, he thought he would serve as an enlightened advisor to an enlightened king, but found that he had been invited as an adornment to the court and was humiliated. Now disillusioned by Frederick the Great of Prussia, Voltaire had no home, no place in life and sunk into despair. His depression deepened with the 1755 earthquake and by his pupil, Frederick the II of Prussia, who plunged Europe into the Seven Years’ War. His deepened despair was furthered by Rousseau’s caustic letter in response to his Poem on the Lisbon earthquake. Voltaire finally settled in Geneva in 1759, where he purchases an estate in Ferney at the French-Swiss border. The years between the Earthquake and publishing of Candide are among the darkest years of his life. The Earthquake, War, European famine, the optimism of the philosophers and the bitterness of the theologians, including Rousseau’s critique of him, all intertwined and nearly killed him with anguish. He wrote to a friend as if it was the end of the world. “People are dying under man made bombardments and famines during siege and the destruction of God’s own nature while the philosophers are saying this is for the best in the best of all possible worlds.”

Voltaire challenged, could not an omnipotent God create a world without such catastrophe and concluded “you do not cure our evils when you deny them in the manner of Leibnizian philosophy.” Life has pain and suffering from nature which is inexplicable and leaves us in such suffering. Voltaire gave his respect to God, but he gave his love to human beings who suffer. What gift can we give to God? What does God not have? God does not have defects, sorrow, ignorance and hope. That is what humans have? Hope! Man’s only bliss is hope. One must choose between a Leibnizian Optimism that denies the existence of evil or the only other choice, the cry of humanistic anguish that admits to evil. In an attempt at the
philosophical explanation for suffering, simply watch a mother dying with her child dying in her arms. To this, the Leibnizian philosopher would state that it is for the best in the best of all possible worlds. Voltaire concluded that evil is real and comprehensible, though God did exist.

For years Voltaire tried to write a piece on optimism in response to Rousseau, then finally his catharsis emerged in the form of his greatest and most influential work over the ages, *Candide*.

The themes of *Candide* are simple and direct. Leibnizian philosophy or any metaphysical philosophy that seeks to deny the reality of natural and physical evil is absurd and irrelevant given the human suffering, the horror wars and natural catastrophes. The one solace human beings have is love. In Voltaire’s usual satirical manner, it is this love that produces syphilis, largely transmitted by clerics in the course of humanity, which in turn gives us slow and painful deaths.

The philosopher says everything is for the best in the best of all possible worlds. *Candide*, who is everyman, is the student of Pangloss, an all-tongue Leibnizian philosopher who gives a reasoned explanation for human suffering or catastrophe on why these events are good things and part of the best of all possible worlds. Such philosophical optimism, Voltaire argues, is fatalism. If whatever is, is right, then whatever will be, is right. Then why work against suffering, war, disease and catastrophe? If whatever is, is right, if whatever happens is the best of all possible worlds, then why intervene in the final analysis? Philosophical and theological optimism are fatalism.

Jacques the Anabaptist, one of the best characters out of Voltaire’s *Candide*, falls overboard while trying to save an ungrateful sailor from drowning in the Lisbon harbor during the Earthquake. As Candide prepares to dive in and save Jacques, Pangloss stops and reasons with Candide. If Jacques drowns, then it was part of God’s plan in this best of all possible worlds. If he drowns it was part of God’s plan, because there is no real evil. This philosophical optimism denies the human reality of irredeemable pain, injustice and cruelty. Candide’s journey is through a landscape of war, arrogance, abuse of power, religious persecutions, colonial degradations, betrayal, disease and despair. Evil is real. If one concludes that there is a God incomprehensible to us, then that is what one must conclude. Human beings are here to care. It is not philosophy, it is the cultivation of the human garden with attention to the real causes of well-being and remediable suffering as the only antidote to despair. It is from abstract philosophy to humanistic activism. Whatever....

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