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Sep. 21, 2013; Hong Kong
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Home Monitoring to Identify Arrhythmia Concerns: The Promise of Personal ECG Screening

By Anatoly Langer, MD, FRCP(C); Asaf Danon, MD, MSc; David Newman, MD, FRCP(C)

Background

As identified by Myerberg et al., efforts to decrease the incidence of out-of-hospital Sudden Cardiac Death (SCD) suffer from an epidemiological paradox.¹ The patients at highest annual risk of SCD represent a very small pool of the total population per year who

had such an event. In effect, the vast majority of SCD occur in those patients in whom cardiac arrest is the first clinical expression of an underlying disease, or those in whom the disease is previously identified, but classified as low risk. Screening for higher risk features in the general population has not been widely adopted though a variety of relatively inexpensive strategies have been proposed. The surface ECG represents a particularly useful tool given that a variety of easily obtainable measures, such as conduction abnormalities (e.g. QRS duration, heart block), QT prolongation, early repolarization and arrhythmia can all be obtained as indicators of potentially modifiable risk. However, the normal range of many of these measures is wide, requiring frequent within-patient measurements. One particularly promising area is the monitoring of the QT interval after medication change.

The QT Interval, Its Measurement and Significance

The QT interval represents the duration of ventricular depolarization and subsequent repolarization, and is measured from the beginning of the QRS complex to the end of the T-wave (see Figure 1). Myocardial cellular repolarization is under exquisite control by a variety of ionic currents that control time and voltage-dependent repolarization processes of the cells of the heart. There is a coordination both between, and within cells, such that the time course of repolarization over the whole

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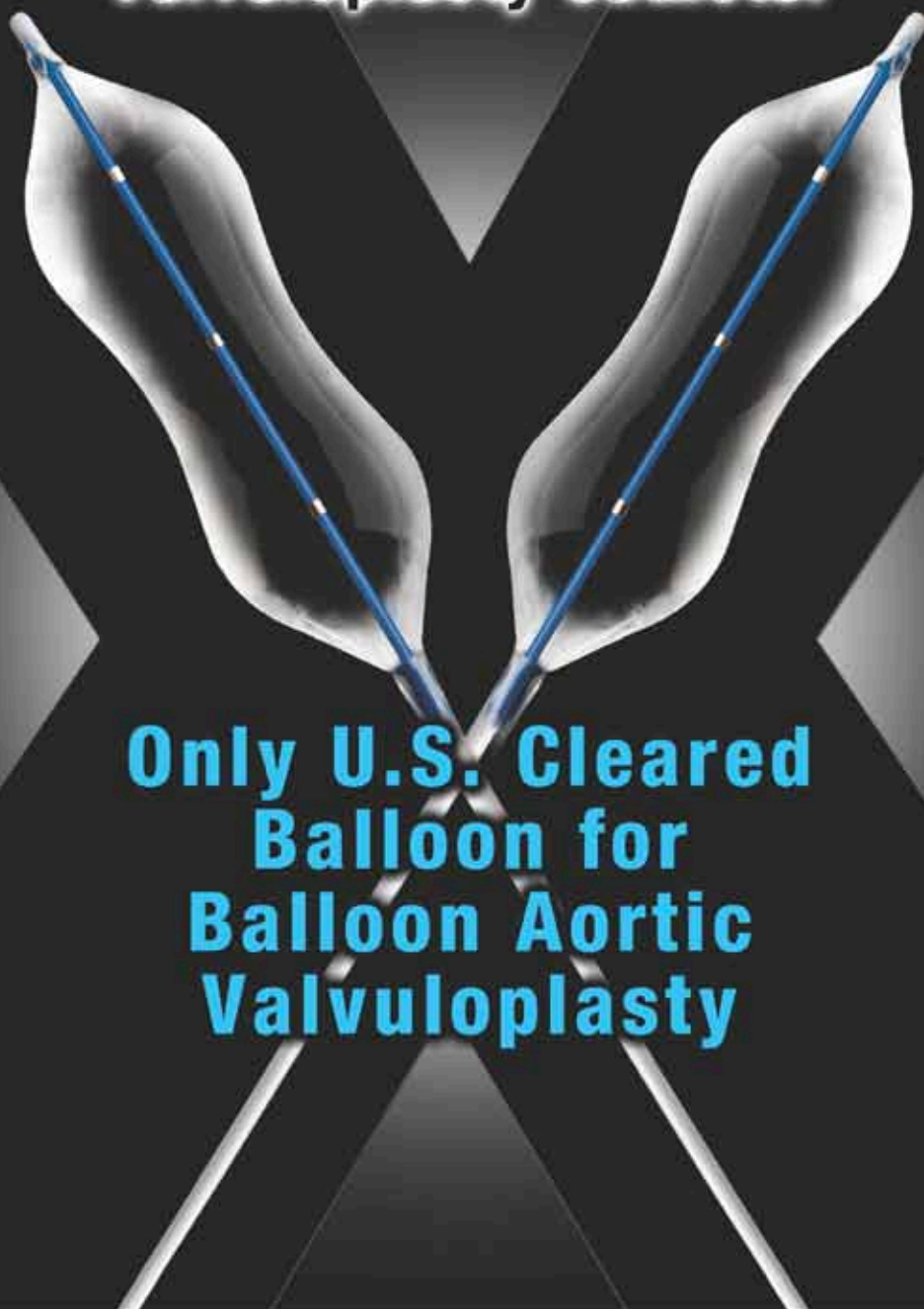
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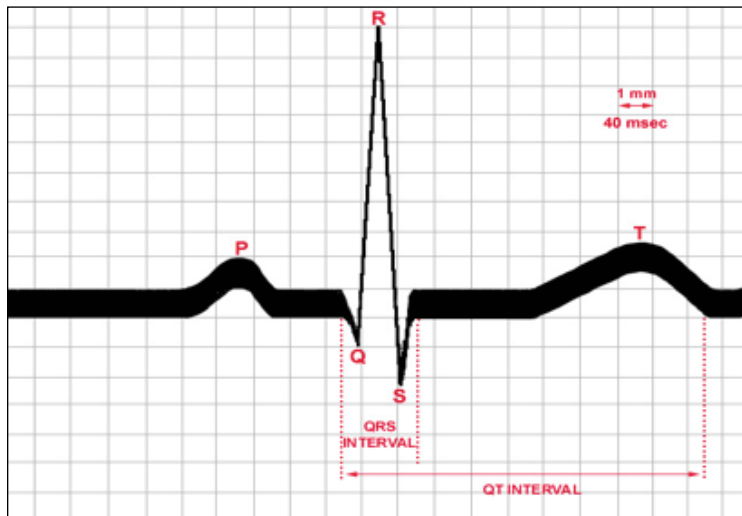


Figure 1. A diagram of an ideal typical lead II ECG tracing to illustrate timing markers. The QT extends from the beginning of the QRS to the end of the T wave. It includes the total activation time of the ventricles. Measurement may not be obvious as illustrated in the diagram.

myocardium is relatively homogenous. If there are significant areas where repolarization is completed while other electrically isolated areas are still depolarized (or partial repolarized), local voltage gradients may be formed and excite, in a heterogeneous fashion, myocardial cells prematurely. When sufficiently deranged, abnormalities of myocardial repolarization as represented on the surface ECG QT interval, may culminate in malignant disorganized ventricular arrhythmias. As conceptually illustrated in Figure 2, the final common pathway for any native (i.e. genetic endowment) disease acquired or drug mediated QT interval prolongation is a predisposition to a polymorphic ventricular tachycardia labeled as Torsades des pointes polymorphic ventricular tachycardia (TdP). This may either self-terminate or degenerate into fatal ventricular fibrillation. Patients who suffer from repolarization-mediated malignant arrhythmias usually have a complex mixture of all three factors, not usually appreciated before events occur.

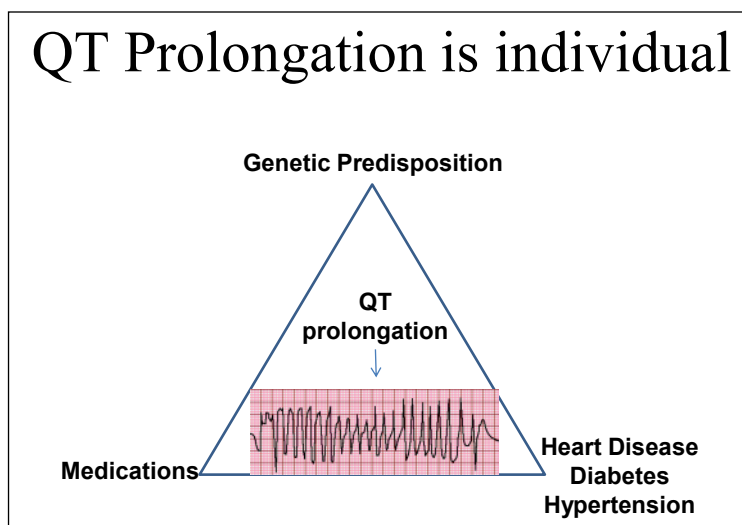


Figure 2. The risk of SCD is composed of combination of genetic predispositions, medication use and underlying heart disease or risk factors for heart disease. For example, genetic predisposition may not be discovered without the effect of medication that increases QT interval.

The normal total myocardial repolarization time as reflected by the QT interval must shorten to allow an increase in heart rate. This has led to a

search for a rate correction algorithm that is reliable and robust able to separate a pathologically prolonged QT interval from normal. Many candidate rate correction formulae have been proposed. For better or worse, the one that has become the standard and established corrects the QT by dividing the measure by the square root of heart rate (Bazett correction). This produces the standard corrected QT or QTc used in all ECG recording systems.

Normal limits for the QTc are well-established, and provide a convenient way to follow individuals:

QTc (msec)	Male	Female
Normal	<430	<450
Borderline	431-450	451-470
Prolonged	>450	>470

While the precision of QT measurement is better when a 12 lead ECG is used, the single lead QT measurement may be more optimal for the monitoring of prolongation of QT given its simplicity of use. As well, some of the technical aspects of concern when assessing the end of the T-wave are mitigated when each patient acts as his/her own control on serial longitudinal measures as long as the same lead configuration is used for each measurement.

Population based QT data:

The relationship between a prolonged QTc interval and the risk of SCD have been studied in a variety of data sets. The Rotterdam Study was a prospective population-based cohort of 3,105 men and 4,878 women aged 55 years and older (see Figure 3).

After a mean follow-up period of 6.7 years, an abnormally prolonged QTc interval (450 ms in men, 470 ms in women) was associated with a three-fold increased risk of SCD (hazard ratio, 2.5; 95% confidence interval, 1.3 to 4.7), after adjustment for age, gender, body mass index, hypertension, cholesterol/high-density lipoprotein ratio, diabetes mellitus, myocardial infarction, heart failure, and heart rate. In patients with an age below the median of 68 years, the corresponding relative risk was 8.0 (95% confidence interval 2.1 to 31.3). The authors concluded that QTc prolongation on the electrocardiogram should be viewed as an independent risk factor for SCD.²

The association between QT interval and cardiovascular morbidity and mortality is well-established.³⁻⁵ QT prolongation has been shown to be predictive of sudden death, and has therefore been advocated as an important screening measure in adults and children.

Drug Induced ECG Effects

Other ECG-derived variables such as the duration of QRS have also been related to the occurrence of sudden death. Relatively few medications not specifically designed for anti-arrhythmic drug effect act to prolong QRS duration by blocking the fast sodium current. Thus, the safety of medications and the potential increase in the risk

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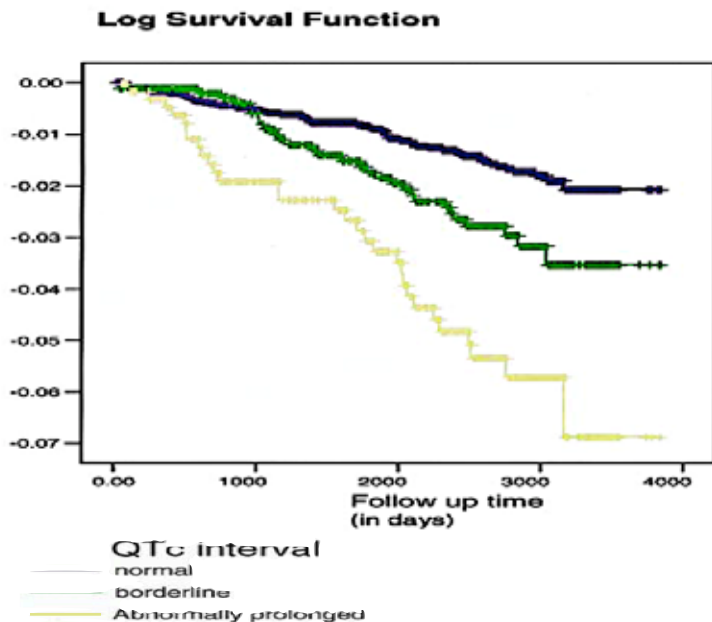


Figure 3. Survival according to QT interval. The graph highlights the incremental risk with QT prolongation.

of sudden death has mostly been raised for QT prolongation and forms the basis for considering longitudinal monitoring.

Drug-induced alterations in cardiac ventricular repolarization may be associated with an increased risk of life-threatening cardiac arrhythmias. As a result of the unpredictable nature of such risks, it is a requirement that all new pharmaceuticals undergo stringent testing to detect potential risk in both normal subjects and the patient population likely to receive the medication.⁶ Drug screening in patients is proceeded by extensive studies in in vitro and in vivo animal models of single cells, isolated heart and whole animal preparations. These attempts to predict dangerous drug effects focus on the main ionic currents responsible for cardiac repolarization, which are the usual culprits predisposing to drug induced long QT related arrhythmias. Similar requirements may also apply for approved drugs when changes in dose, route of administration, indication or patient population are contemplated. The website of the International Registry for Drug-Induced Arrhythmias, maintained by the Georgetown University (www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm), provides an up-to-date list of drugs that are classified as highly likely, possible or unknown agents on their effect on the QTc interval and/or risk for induction of TdP or ventricular arrhythmia.⁷ Importantly, there is a disclaimer on the site:

Drugs not listed here may have an, as yet, undetected potential to prolong the QT interval or induce Torsades de pointes. Not all drugs have been adequately tested for this potential. Therefore, the absence of a drug from these lists should not be considered an indication that they are free of risk of QT prolongation or Torsades de pointes.



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Drug-induced QT prolongation may be affected by other factors including: genetic mutations and polymorphism, metabolic derangements, gender and others. Some of the medications that may cause QT prolongation are listed in Table 1. There are two caveats for this effect: first, some of the drugs prolong QT, but rarely cause TdP (Amiodarone, Verapamil) due to other effects (e.g., blockade of other ionic channels; second, any drug effect is highly individualized and generally quite rare. As illustrated in Figure 2, the transition from a drug-induced long QT to overt Tdp or sudden death risk, may be further enhanced by acquired metabolic or known clinical risk factors such as bradycardia, diuretic induced changes in potassium or magnesium metabolism, female gender, metabolic inhibitors, other QT prolonging drugs, underlying heart disease (CHF, LVH, AF), stroke, diabetes, and genetic

Table 1 - Medications That May Increase QT Interval

High Risk	Disopyramide Dofetilide Ibutilide Procainamide Quinidine Sotalol Bepidil
Medium Risk	Amiodarone Arsenic trioxide Cisapride Calcium-Channel Blockers: lidoflazine Antibiotic Agents: Azithromycin, Clarithromycin, Erythromycin, Halofantrine, Pentamidine, Moxifloxacin, Sparfloxacin Antiemetic Agents: Domperidone, Droperidol Antipsychotic Agents: Hhlorpromazine, Haloperidol, Mesoridazine, Thioridazine, Pimozide, Methadone

polymorphism.

Recently, two large studies examined the relationship of antibiotic usage and Sudden Death (SD). Ray et al. found an increased SD rate with Azithromycin in large US data base.⁸ Not all such studies agree; Svanström et al. assessed the same relationship in Denmark, but found no increased risk of SD with this medication.⁹ Both studies were done carefully and included a very large number of patients. The difference in the study conclusions may lie in the variation between the populations, including genetic background and other cardiovascular risk factors. The implication is clear: commonly used antibiotics may warrant concern in predisposed populations. Such post-marketing identification of long QT mediated risks for sudden death are usually at such low prevalence that they are not appreciated until after market release has occurred. Regulators then respond either by stopping distribution of the drug, as in the pro-motility drug Cisapride. The more common response is issuing a so called 'black-box' warning to prescribers, as has now occurred for: Ritalin derivatives in the management of pediatric ADHD, Citalopram at high dose in the management of depression,

and Azithromycin. Lastly, for highly restricted drugs such as Methadone, follow physician advisories/ practice guidelines, or change to safer alternatives are used or mandated.

Federal Drug Agency (FDA) Guidelines: Why Measure and Follow QT/QTc⁶

While the degree of QT prolongation is recognized as an imperfect biomarker for proarrhythmic risk, in general there is a qualitative relationship between QT prolongation and the risk of TdP, especially for drugs that cause substantial prolongation of the QT interval. It is not clear, however, whether arrhythmia development is more closely related to an increase in the absolute QT interval or QTc. Most drugs that have caused TdP clearly increase both the absolute QT and the QTc (hereafter called QT/QTc). From a population perspective, the FDA has determined that changes of as little of 5 ms may be clinically relevant. The FDA has stated that mean QT prolongation of more than 20 ms have substantial arrhythmia risk. Nevertheless, even smaller mean prolongation may be pro-arrhythmic. This is because any drug-mediated QT prolongation is a result of the interaction between the medication and patient variables including genetic background, drug interaction with other medications, electrolytes and heart rate. Some of these parameters are dynamic and, therefore, the QT measurements may give dynamic values. Thus, the mean value may not reflect the risk in individualized patients. Indeed, some non-cardiovascular drugs that have been withdrawn from the market because they cause SCD, result in a mean increase in the QT interval as small as 5 to 10 msec in populations of patients.^{10,11}

From a Population to the Individual: the Potential Role of Home Monitoring

The risk is variable and the optimal method of monitoring is unknown. Phenotypic screening using QT measurements is standard and simple, and may be the simplest to deploy. However, QT measurements are dynamic, and not always correlated with increased risk.

The FDA mandates that all new drugs undergo testing to ensure that there is no QT prolongation; however, the QT testing is normally done in healthy volunteers, and never for prolonged periods of time. Since new drugs are tested in only a few thousand patients for approval, the fact that no cases of TdP have been

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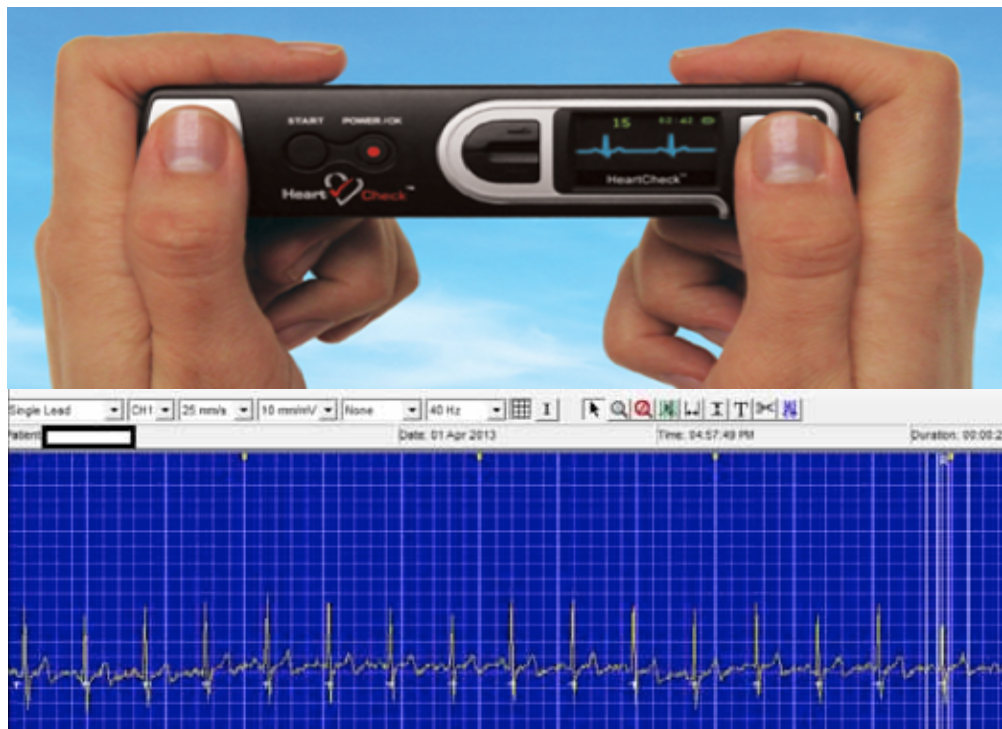
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Figure 4.

A: An example of an FDA cleared commercially available consumer ECG recording system (the HeartCheck™ PEN ECG; CardioComm Solutions, Inc., CANADA). The device weighs 60g. The patient acts as his or her own control and the ECG recording lead configuration (vector) is always the same. The digitally acquired ECG data is sent to a core ECG laboratory for expert interpretation and a report provided back to the consumer/patient within 30 minutes.

B: An example of actual patient recorded data using the device illustrated in A above. In this case a patient recorded his/her rhythm at home before psychotropic medication for ADHD. Over time any concerning metabolic effects on QT can be trended with the patient acting as his own control. The system automatically identified the peak of the QRS complex and computes the heart rate from R-R interval. The technician reading the transmitted data places calipers for recording of PR, QRS and QT intervals, with automatic calculation of the Bazett formula rate corrected QTc.

observed before a drug is approved is not very informative; even if no cases are recorded in a data base including 5000 patients, the 95% confidence interval for the risk of TdP would be 0 to 1 in 1600 — with the upper limit reflecting the potential for a relatively high incidence post-marketing prevalence.¹¹

Thus, there may be a need for a dynamic and individualized monitoring of the QT when introducing a new drug. One option may be a small hand held device that records a single lead ECG for patient screening while taking a drug. An example of such a device and the downloaded data obtained is illustrated in Figure 4. Such a device always records the same ECG lead configuration and allows each patient to act as his/her own control for serial measures. To increase specificity, this can also be standardized to standardized time of day. The potential utility of such a system for drug monitoring has not been formally studied, but may have promise to act as a

screen which then would trigger further investigations as needed, especially on frequently used medications with any index of concern, perhaps driven by changes in metabolic or hemodynamic status or co-administration of medications or for any other reason.

Genetic Predisposition

It is estimated that 5-10% of patients suffering TdP have, in fact, subclinical congenital Long-QT Syndrome (LQTS). These patients have one of the well-known rare genetic mutations that result in QT prolongation.¹² However, there may be other genetic malformations that were not linked to LQTS, either because their effect is smaller or that their prevalence in the population is much higher. Using Genome Wide Association (GWA) studies, it is possible to track these genes. Arking et al. used the QT as a marker for these genes.¹³ They performed a GWA study on healthy individuals, and linked long QT with common

(>5% of normal people) single nucleotide polymorphism (SNP). Using this method, they were able to identify a common variant of NOS1AP gene that occurs in 60% of population, and may be responsible for up to 1.5% of QT variation. Volpi et al. performed similar study of psychiatric patients taking the novel atypical antipsychotic drug, loperidone, in a phase III study. After performing GWA study of the patients, they were able to link 6 common SNPs to QT prolongation measured 14 days after introducing the medication.¹⁴

Conclusion and Future Perspective

Policy-driven, increased post-marketing surveillance, and advances in such epidemiological tools, as linked administrative data bases, have allowed an increased appreciation that many commonly used medications may, in predisposed individuals, harbor risk for the development of potential lethal arrhythmias. How to more clearly identify and risk-stratify patients “at risk” remains a compelling problem.

One approach may be personalized serial phenotypic assessment by home monitoring of the QTc or other ECG based signals. Such technology is relatively simple and easily available. Its exact role is as yet unclear; however, the ease of use may well promote general use of such tools especially for patients on drugs of concern who are also vulnerable either by disease or in the setting of the often unknown risks of polypharmacy.

Advances in whole genome assay measures, while more remote and not as easily available, may help to characterize further or increase pools of risk for which more detailed phenotypic screening may be of particular value. The future challenge may be in the combination of both tools for personalized medicine applications. It may be possible to determine very low-risk population that requires no monitoring at all. Others will be monitored for a phenotypic signal, likely QTc/QT prolongation. Monitoring may be done dynamically and analyzed semi-automatically to trigger more enhanced referral and evaluation. The future safety of drug administration may be maximized by the use of these approaches.

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“Advances in whole genome assay measures, while more remote and not as easily available, may help to characterize further or increase pools of risk for which more detailed phenotypic screening may be of particular value. The future challenge may be in the combination of both tools for personalized medicine applications.”

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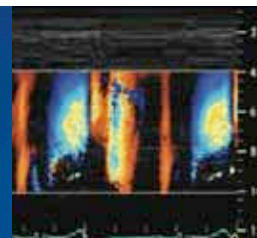
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Pediatric Pulmonary Arterial Hypertension Survey (PPAHS): Beliefs and Practice Among Physicians on the Use of Phosphodiesterase Inhibitor (Sildenafil)

By Varun Aggarwal, MD; Danyal Khan, MD

Keywords: Pulmonary arterial hypertension, Sildenafil, FDA, children

Abbreviations: FDA: Food and Drug Administration, PPAHS: Pediatric Pulmonary Arterial Hypertension Survey, PAH: Pulmonary Arterial Hypertension, cGMP: cyclic guanosine monophosphate, PDE: phosphodiesterase, PPHN: persistent pulmonary hypertension of the newborn, iNO: inhaled Nitric Oxide

Introduction

The development of the compound Sildenafil dates back to 1986 when the chemists of the Pfizer company were working on a compound to treat hypertension. They chose to target augmentation of the renal tubular activity of atrial natriuretic peptide through its second messenger, cyclic guanosine monophosphate (cGMP), and the phosphodiesterase (PDE) family of enzymes. Test compounds were shown to antagonize the activity of PDE,⁵ resulting in vasodilatation and platelet inhibition, diverting the researcher focus for management of angina. Clinical trials done subsequently in angina patients were disappointing, but some patients reported the surprising and unexpected side effect of penile erection leading to use of the compound for the management of erectile dysfunction. As a better insight into the mechanism of action of Sildenafil evolved, its role in management of pulmonary hypertension (PAH) was postulated, eventually leading to its use in the management of this condition.¹

Most of the studies for the management of PAH are done in adults, and many of these medications are commonly used in children on an off-label basis due to the life-threatening nature of PAH. Although approved for use in adult PAH by Food and Drug Administration (FDA) in June 2005, off-label Sildenafil is used extensively for the treatment of neonates, infants and children with PAH. Past studies have generally suggested favorable effects and outcomes in infants and young children with PAH, but these reports are generally uncontrolled observations, except for one single center trial for persistent pulmonary hypertension of the newborn.² Despite extensive clinical experience with Sildenafil therapy in children and approval for its pediatric use in Europe, the FDA (on August 30, 2012) issued a warning³ against the use of Sildenafil for pediatric PAH between 1 and 17 years of age due to an apparent increase in mortality during long-term therapy. We aim to describe the utilization rates, trends, and attitudes toward Sildenafil among practicing physicians.

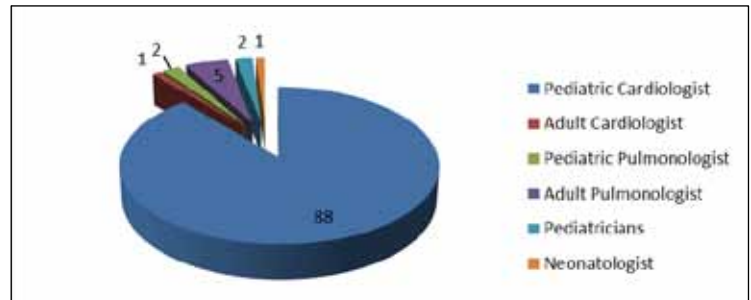
Methods

In September 2012, we designed a survey regarding Sildenafil use in children. This survey was hosted on the 'SurveyMonkey.com' website. The survey contained nine questions and average time estimated to complete the survey was about 3 minutes. An email was sent to two email forums of Pulmonary Hypertension Association (PHA) – (PHAdoctors@yahoogroups.com) and PediheartNet (pediheartnet@googlegroups.com) with a link to the questionnaire on the Survey Monkey website. Pulmonary Hypertension Association (PHA) doctors is a discussion forum for medical doctors (MDs and DOs) interested in expanding discussion of the medical issues relating to diagnosis and treatment of pulmonary hypertension and current research of this illness. It was founded in May 2000 and has 554 members. PediHeartNet was started in 1994 and currently has over 1,500 members from over 60 countries. The vast majority of members are cardiologists and cardiac surgeons, but a variety of other professionals are represented.

Results

Out of physicians who were sent the link to participate in the survey, 100 physicians responded to the survey. Details of the Pediatric use of Sildenafil survey results are as follows:

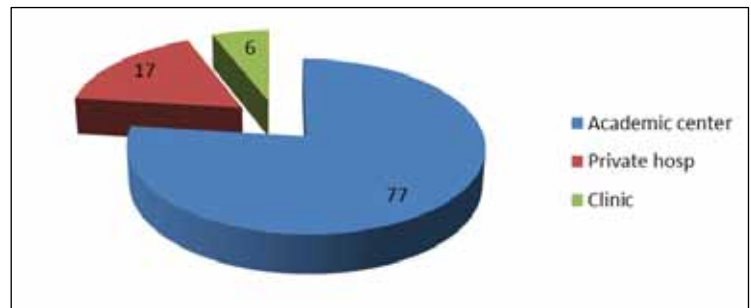
Total number of respondents: 100



Question 1

Q.1 Respondents by profession are:

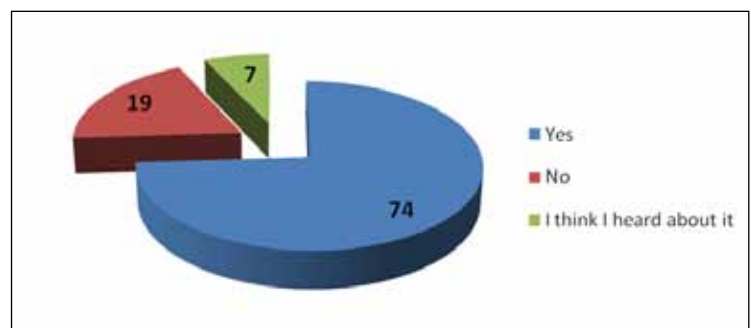
- Pediatric Cardiologists 88%
- Adult Cardiologists 1%
- Pediatric Pulmonologists 2%
- Adult Pulmonologists 5%
- Other 4%



Question 2

Q.2 I work in a:

- Academic Hospital 77%
- Private Hospital 17%
- Clinic 6%



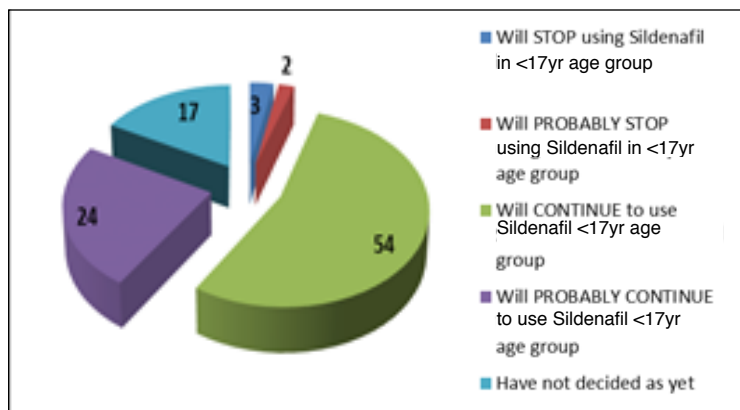
Question 3

Q.3 Are you aware that the FDA on 8/30/2012, (based on a double blind placebo controlled study published in *Circulation* in January 2012) issued a warning stating that, "the use of Revatio (Sildenafil) is not recommended in Pediatric patients (1-17 yrs age)?"

- Yes 74%
- No 19%
- I think I heard about it 7%

Q.4 Are you aware that abruptly stopping Sildenafil (Revatio) could lead to significant clinical worsening?

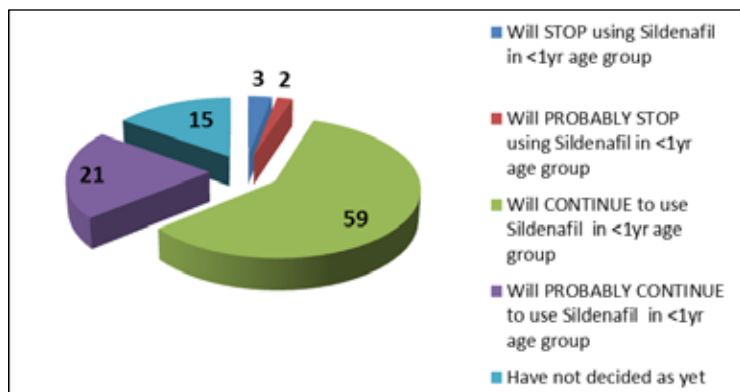
- Yes 91%
- No 6%
- I think I know about it 3%



Question 5

Q.5 Are you planning to stop using Sildenafil in the 1-17 yr age group?

- Will STOP using Sildenafil in 1-17yrs age group - 3%
- Will PROBABLY STOP using Sildenafil in 1-17 yrs age group - 2%
- Will CONTINUE to use Sildenafil in 1-17 yrs age group - 54%
- Will PROBABLY CONTINUE to use Sildenafil in 1-17 yrs age group - 24%
- Have not decided as yet - 17%



Question 6

Q.6. Are you planning to stop using Sildenafil in the <1 yr age group? (since the FDA recommendations are for the 1-17 yr age group and do not address the less than <1 yr age group)

- Will STOP using Sildenafil in <1 yr age group - 3%
- Will PROBABLY STOP using Sildenafil in <1 yr age group - 2%
- Will CONTINUE to use Sildenafil in <1 yr age group - 59%
- Will PROBABLY CONTINUE to use Sildenafil in <1 yr age group - 21%
- Have not decided as yet - 15%

Q.7. Do you currently prescribe Tadalafil (Adcirca) in the Pediatric age group?

- Yes 28%
- No 72%

Q.8. Are you more likely to prescribe Tadalafil (Adcirca) in the Pediatric age group now (in light of FDA's warning against use of Sildenafil/Revatio in Pediatric patients)?

- Yes 31%
- No 69%

Q.9. Are you more likely to prescribe Bosentan (Tracleer) to patients in the Pediatric age group, whom you would have previously prescribed Sildenafil/Revatio to (in light of FDA's warning against use of Sildenafil/Revatio in Pediatric patients)?

- Yes 42%
- No 58%

Discussion

Sildenafil was first approved for use for erectile dysfunction in March 1998, and PAH in adults in June 2005. Though Sildenafil has never been approved for the treatment in children, off-label use is very common for PAH in children. In 1999 Atz AM, et al⁴ reported the first clinical use of Sildenafil in children to facilitate weaning from iNO following corrective surgery for congenital heart disease. Namachivayam P, et al⁵ reported that a single dose of Sildenafil prevented rebound after withdrawal of NO, and reduced the duration of mechanical ventilation. A small trial done in newborns with PPHN showed a dramatic improvement in oxygenation and survival.⁶

Sildenafil has been commonly used off-label in children with PAH. Based on the recent large randomized controlled trial on the use of Sildenafil in children with PAH,⁷ the FDA recently released a strong warning against the use of Sildenafil for children aged 1-17 years.³

We present here the beliefs and practice reported by 100 US physicians after the FDA warning issued on Aug 30th 2012. The survey was sent to the physicians on Sept 10th 2012. Eighty-one percent of the physicians have heard about the warning possibly due to wide spread emails and personal communications by Pfizer and FDA. The majority of the physicians were aware of the possible sudden worsening on abrupt withdrawal of Sildenafil. It was surprising to note that only 5% of physicians said that they will "stop" or "probably stop" Sildenafil in children <1 year and 1-17 years. This might be because Sildenafil is probably the most prescribed oral medicine for PAH in the pediatric age group, and that pediatric physicians have become comfortable with its use. However, apart from Nitric Oxide, there is no oral, parenteral or inhaled medicines for PAH that are approved by the FDA for pediatric use.

Tadalafil, another relatively new PDE inhibitor (approved by FDA for use in adults with PAH in 2009), is currently used by less than 1/3 of the physicians who responded to the survey. Thirty-one percent of the physicians are more likely to prescribe Tadalafil after the FDA warning. We are concerned as both Sildenafil and Tadalafil belong to the same class, and Sildenafil has been studied less extensively both in studies and clinical medicine. Nearly half (42%) will now use bosentan which is also a relatively less well used medicine.

The randomized controlled trial (RCT) used as a reference by FDA for the warning is called STARTS-1.⁷ It evaluated the role of Sildenafil at low, medium and high doses in 'treatment-naïve' children with PAH. The patients were randomized to placebo or either one of the three treatment groups for 16 weeks. The primary endpoint of improvement in peak oxygen consumption during exercise testing was found to be only marginally different between Sildenafil (all three groups combined) and placebo ($p=0.056$), but greater effect was noted in the medium and high dose groups when compared to the placebo. The adverse effects reported in the 16 week study were headache, pyrexia, upper respiratory infection, vomiting and diarrhea. Eleven patients reported severe adverse events, and two were considered to be treatment-related (both in high dose treatment group: stridor and ventricular arrhythmia). Patients who completed the 16 week trial were eligible to receive Sildenafil for extended

“Despite the concerns expressed by the FDA on the safety of Sildenafil, based on the results of the same study, the European Medicines Agency (EMA) has approved Sildenafil for pediatric PAH. The dosage recommended by the agency is: for children <20 kg- 10 mg three times a day and for children >20 kg- 20 mg three times a day..”

treatment (STARTS- 2). For patients > 20 kg, the three year survival in low dose, medium dose and high dose Sildenafil was 92%, 90% and 84% respectively. For children <20 kg, the three year survival was 93% and 94% in the medium and high dose groups respectively. A total of 35 deaths were reported during the treatment or follow-up. The reported incidence of deaths was 9%, 14% and 20% for patients randomized in STARTS-1 or -2 to low, medium and high dose Sildenafil respectively. A direct dose effect on mortality was observed with the highest dose having the worst outcome. The hazard ratio for high dose compared to low dose was 3.5 (p=0.015). The FDA issued their warning based on these high rates of mortality noticed in the higher dose groups.

Although there was no placebo arm in the follow-up study (STARTS-2), the investigators reported that the survival rates compared favorably with historical rates. The three year survival rates for pediatric PAH patients before the availability of PAH-specific therapy was 33 to 52%. Also, the authors have reported that the baseline characteristics were not similar in patients who died and those who were alive. Of the patients who died, 74%, 69% and 71% had baseline values above median for PVRI, mPAP and right atrial pressure respectively. Forty percent of the patients who died were classified as FCIII

or IV at baseline as compared to 15% in the overall study group. Eighty percent of the patients who died had baseline N-terminal-pro-brain natriuretic peptide levels above the median (as compared to 44% of the patients still alive).

Despite the concerns expressed by the FDA on the safety of Sildenafil, based on the results of the same study, the European Medicines Agency (EMA) has approved Sildenafil for pediatric PAH. The dosage recommended by the agency is: for children <20 kg- 10 mg three times a day and for children >20 kg- 20 mg three times a day.

Abman SH et al⁸ recently reviewed the implications of the FDA warning. They recommended that all prescribing physicians should contact families of children with PAH who are on Sildenafil, and discuss the potential risks and benefits. Adjustments may be made in the dose of Sildenafil in accordance with EMA-approved dosing. They also recommended against sudden withdrawal of Sildenafil, as there is a risk of sudden deterioration. Although low and medium doses of Sildenafil seem likely safe in treating pediatric PAH, further studies should carefully examine its role in the long-term therapy of children, especially with diverse causes of PAH. Pediatric patients with PAH require close surveillance and frequent monitoring until further data is available.

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Letters to the Editor

Do you have comments or topics you would like to address, please send an email to: LTE@CCT.bz, and let us know if you would like your comment published or not.

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Image of the Month #6 - July 2013 - Presented by The Archiving Working Group

Contributors: Jorge M. Giroud, MD; Robert Anderson, MD; Vera D. Aiello, MD; Diane E. Spicer, BS; Jeffrey P. Jacobs, MD

This is a special column that is published bimonthly in *Congenital Cardiology Today* with contributors and images from the Archiving Working Group (AWG) of the International Society for Nomenclature of Paediatric and Congenital Heart Disease.

Please visit us at the AWG Web Portal at <http://ipccc-awg.net> and help in the efforts of the Archiving Working Group and the International Society for Nomenclature of Paediatric and Congenital Heart Disease.

The authors would like to acknowledge the Children's Heart Foundation (www.childrensheartfoundation.org) for financial support of the AWG Web Portal.

IPCCC:

07.15.04, 07.11.05, 07.10.01, 07.13.05, 01.01.18

AEPC Derived Term:

Multiple VSDs (07.15.04)

Muscular VSD: multiple trabecular (Swiss cheese) (07.11.05)

Perimembranous VSD (07.10.01)

VSD in double outlet VA connection: subpulmonary (07.13.05)

Double outlet right ventricle: transposition type (subpulmonary VSD) (01.01.18)

EACTS-STC Derived Term:

SD, Multiple (07.15.04)

VSD, Type 4 (Muscular), Multiple - "Swiss-Cheese" (07.11.05)

VSD, Type 2 (Perimembranous) (Paramembranous)

(Conoventricular) (07.10.01)

VA connection =Double outlet VA connections-modifier for VSD in double outlet VA connection, Subpulmonary (07.13.05)

DORV, "TGA type" (Subpulmonary VSD) (01.01.18)

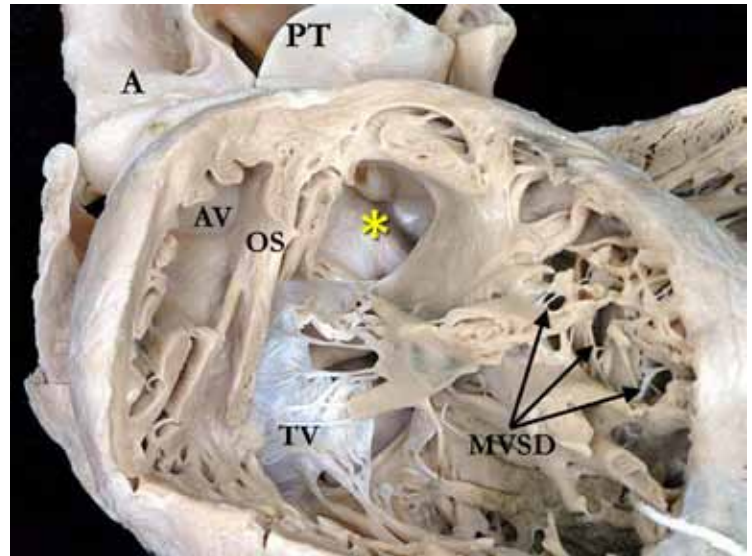
ICD10 Derived Term:

Ventricular septal defect (Q21.0)

Double outlet right ventricle (Q20.1)

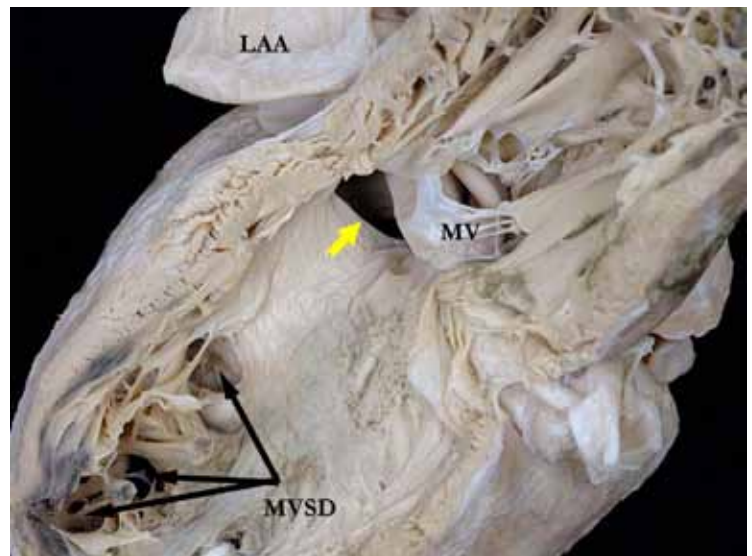
Discussion:

The images of the specimen chosen for this month's discussion demonstrate the problems still existing in describing and classifying holes between the ventricles. The major feature of the heart shown in this, the sixth "Image of the Month" column, is that the major deficiency in ventricular septation is located directly beneath the right ventricular origin of the pulmonary trunk, in addition to the multiple defects present in the muscular apical septum. The pulmonary valve itself is primarily supported by right ventricular musculature, but its posterior leaflets are in fibrous continuity with the anterior leaflet of the mitral valve. There is also fibrous continuity in the postero-inferior corner of the major area of septal deficiency between the leaflets of the pulmonary and tricuspid valves. It is this feature that permits the defect to be considered as being perimembranous, since the atrioventricular component of the membranous septum is part of this area of fibrous continuity. The geographical location of the defect, in directly subpulmonary position, also justifies placing the specimen itself within the spectrum of lesions described as the Taussig-Bing malformation. The question arises, however, as to whether the septal deficiency itself is justifiably described as a "ventricular septal defect?" This point is further illustrated by the



Description: The outlet components and septal surface of this heart with double outlet right ventricle are viewed from the apex. The aorta (A) is anterior and to the right of the pulmonary trunk (PT). The aortic valve (AV) is supported by a complete muscular infundibulum, and the pulmonary valve lies above a perimembranous interventricular communication (yellow asterisk). The muscular outlet septum (OS) lies completely within the right ventricle. The tricuspid valve (TV) guards the inlet of this morphologically right ventricle, and is in fibrous continuity with the pulmonary valve. At the apex there are multiple, muscular ventricular septal defects (MVSD).

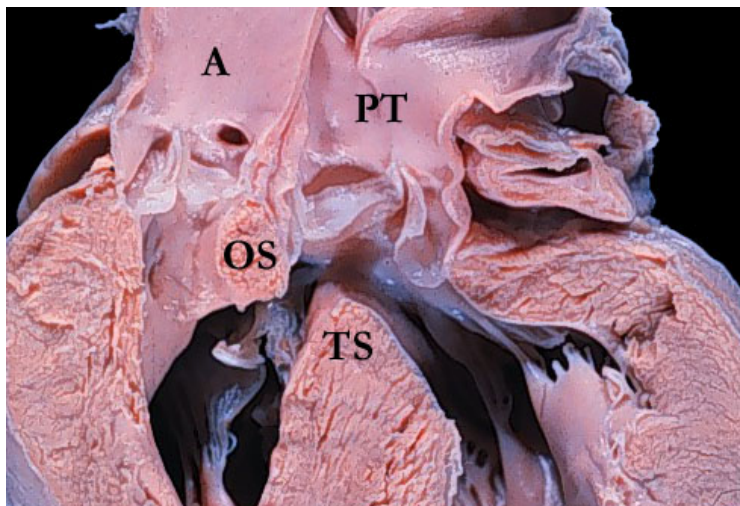
Contributor: Diane E. Spicer, BS



Description: The left ventricle of the heart shown in the upper panel is opened in a clam-shell fashion demonstrating the muscular apical margin (yellow arrow) of the perimembranous interventricular communication, and the multiple, apical, muscular ventricular septal defects (MVSD). The mitral valve (MV) guards the inlet of this morphologically left ventricle. (LAA-left atrial appendage)

Contributor: Diane E. Spicer, BS

AWG Web Portal link for this series of images: http://ipccc-awg.net/VSD_Page/VSD_Multiple_07_15_04/VSD_Multiple_07_15_04.htm



The ventricular outlets appear in parallel, with the aorta (A) arising from the right ventricle. The pulmonary trunk (PT) overrides the apical trabecular septum (TS), but is predominantly connected to the left ventricle. There is malalignment of the outlet septum (OS), which lies exclusively inside the right ventricle. There are discordant ventriculoarterial connections.

image within this discussion (provided by Dr. Aiello) and complements the "Images of the Month." It shows that the muscular outlet septum, which separates the subaortic and subpulmonary outflow tracts, is exclusively positioned within the right ventricle. A strong case can be made, therefore, for considering the plane of space between the inferior margin of the outlet septum and the crest of the muscular septum as the "ventricular septal defect." And, of course, it would be this plane that would be closed by the cardiac surgeon so as to reconnect the subpulmonary outflow tract with the left ventricle, this procedure, along with an arterial switch, being necessary to produce biventricular repair had surgical treatment been attempted during the life of the patient. It would obviously have been a disaster had the hole directly beneath the pulmonary valve in the patient with double outlet right ventricle been closed during any attempted surgical repair. For all these reasons, it is our belief that the major hole under consideration in our "Image of the Month," marked by the yellow asterisk, is better described as an interventricular communication, rather than a ventricular septal defect. The additional multiple defects with the muscular apical septum produce the so-called "Swiss-cheese septum."

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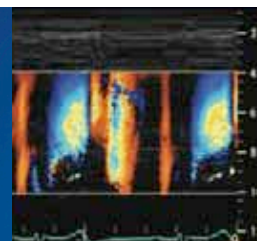
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Medical News, Products and Information

Two Real-World European Studies of Abbott's Minimally Invasive MitraClip® Device Demonstrate Positive Outcomes for Patients with Mitral Regurgitation

In June, Abbott announced publication of positive outcomes from two European post-approval studies of the first-in-class catheter-based MitraClip® therapy for the treatment of mitral regurgitation (MR). Results from ACCESS-EU, a European prospective study that enrolled 567 patients at 14 sites, have been published in the *Journal of the American College of Cardiology*. In addition, findings of the investigator-sponsored German TRANscatheter Mitral Valve Interventions (TRAMI) registry, which enrolled 1,064 patients at 20 German sites, were recently published in *EuroIntervention*.

Abbott's MitraClip System, which received CE Mark in 2008, and is commercially available in Europe and other international markets, is an investigational device in the United States. The device is delivered to the heart through the femoral vein, a blood vessel in the leg, and is designed to reduce MR by clipping together a portion of the leaflets of the mitral valve to allow the heart to more efficiently pump blood.

Data from ACCESS-EU demonstrated that in real-world, post-approval experience in Europe, patients undergoing the MitraClip therapy are predominantly high surgical-risk, elderly patients who are mainly affected by functional MR, a type of MR in which a damaged heart impairs the performance of a normal mitral valve. ACCESS-EU showed that in this patient population, the MitraClip procedure demonstrated low rates of hospital mortality and adverse events and provided significant improvements in day-to-day quality of life at one year following treatment.

"I am impressed by the excellent outcomes observed in real-world patients with the MitraClip therapy. The procedure proved safe and effective even in patients who are at high-risk for complications from mitral valve surgery," said Francesco Maisano, MD, Director of Transcatheter Valve Therapies at San Raffaele Hospital in Milan, Italy, lead author of the ACCESS-EU data publication and co-principal investigator of the study. "In my experience, the MitraClip therapy has a definite role for patients who are not candidates for surgery. I have treated many patients who have experienced a dramatic improvement in quality of life. Relief from the symptoms of mitral regurgitation has allowed many bedridden patients to return to normal day-to-day activities."

"The data from these studies, which together evaluated more than 1,600 patients, add to the clinical evidence confirming positive results for treatment with MitraClip in high surgical risk patients suffering from the debilitating symptoms of significant mitral regurgitation," said Charles A. Simonton, MD, FACC, FSCAI, Divisional Vice President, Medical Affairs, and Chief Medical Officer, Abbott Vascular. "The MitraClip device represents a true advance for these patients, who suffer from poor quality of life and have no satisfactory options to reduce their significant mitral regurgitation."

Findings of the ACCESS-EU study showed:

- Most patients currently treated in Europe are high surgical risk. The mean age was 74 years, with 45% of patients older than 75 years. Most patients had secondary or functional mitral regurgitation (FMR), a type of MR in which a damaged heart impairs the performance of a normal mitral valve; low ejection fraction (most 40% or lower); and presented with multiple comorbidities, including coronary artery disease (63%), hypertension (76%), atrial fibrillation (68%) and renal disease (42%).
- An implant success rate of 99.6%.
- No incidence of death or stroke during the MitraClip procedure and in the immediate post-operative period.
- A majority of patients (91.2%) achieved MR reduction to MR grade of 2+ or less (on a scale of 1+ [mild MR] to 4+ [severe MR]) at discharge ($p < 0.0001$).
- At one year following the procedure, 78.9% of patients were free from MR severity of 2+ or more ($p < 0.0001$), and 71.4% of patients were in NYHA Functional Class II or Class I compared to 15% at baseline ($p < 0.0001$).
- A large majority of patients (79.2%) were discharged to home rather than to a skilled nursing facility.
- Significant improvements in quality of life. At one year, Six-Minute Walk Test results, which measure distance walked on a flat, hard surface in a six-minute period, improved by a mean of 59.5 meters ($p < 0.0001$). Minnesota Living With Heart Failure results, which measure the effects of symptoms, functional limitations and psychological distress on an individual's quality of life, improved by a mean 13.5 points ($p < 0.0001$).

Results of the TRAMI registry showed similar benefits for the MitraClip therapy in both elderly and younger patients. To evaluate the influence of age, patients were divided into two subgroups: patients 76 years old and above, and patients younger than 76 years of age. The procedure proved to be safe in both groups. Hospital mortality was 2.9% in elderly patients and 2.8% in younger patients ($p = 0.96$). Major adverse cardiovascular or cerebrovascular events (MACCE), defined as a composite endpoint of death, myocardial infarction or stroke, was 3.5% vs. 3.4% ($p = 0.93$) respectively. The majority of patients – 81.8% of elderly patients and 86.2% of younger patients ($p = 0.06$) – fully recovered from the MitraClip procedure and were discharged without the need for nursing care. There was substantial relief of heart failure symptoms for the majority of patients, with comparable proportions of patients in NYHA Functional Class II or Class I (69.5% and 61.4%, respectively; $p = n.s.$).

Mitral regurgitation (MR) is the most common type of heart valve insufficiency, affecting approximately one in 10 people aged 75 years and older. The condition occurs when the leaflets of the mitral valve do not close completely, causing blood to flow backward and leak into the left atrium of the heart during the cardiac cycle. To maintain an adequate forward flow of blood throughout the body, the heart compensates by increasing the size of the left ventricle, the main pumping chamber of the heart. This requires the heart to work harder,

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and may ultimately lead to irregular heartbeats, stroke, heart attack or death. MR may also lead to heart failure, a potentially deadly condition that occurs when the heart is unable to pump sufficiently to distribute blood flow to meet the needs of the body.

Abbott's MitraClip therapy is designed to reduce MR and provide clinical and quality-of-life benefits for patients suffering from the debilitating symptoms of significant MR by clipping together a portion of the leaflets of the mitral valve. The device is delivered to the heart through the femoral vein, a blood vessel in the leg. The heart beats normally during the procedure, and a heart-lung bypass machine is not required. By reducing MR, the therapy may allow the heart to recover from overwork and improve function, potentially halting the progression of heart failure and enabling patients to live a higher-quality life.

The device received CE Mark in 2008 and is commercially available in approximately 30 countries, with more than 9,000 patients treated to date. The European Society of Cardiology (ESC) 2012 heart failure guidelines, and the ESC/European Association for Cardio-Thoracic Surgery 2012 guidelines for the management of valvular heart disease specify the MitraClip device as a treatment option for high-surgical risk patients with MR.

For more information, go to: www.abbott.com.

The Barth Syndrome Foundation, Inc. (BSF) 2013 Request for Research Proposals and Changes to the Research Grant Program

The Barth Syndrome Foundation, Inc. (BSF) and its international affiliates are pleased to announce the availability of funding for basic science and clinical research on the natural history, biochemical basis, and treatment of Barth Syndrome. Starting in 2013 there will be two types of grant awards: IDEA grants for 1-2 years and DEVELOPMENT grants for 2-3 years with budgetary maximums of USD \$50,000 or \$100,000, respectively over the full period. BSF's Research Grant Program allows young, non-tenured investigators to include in their submitted budget up to 75% of the direct costs amount as PI salary (10% for

established investigators). In addition, for those clinical applications where volunteers must travel to a clinical research site, these travel expenses will be handled separately and will not be included in the application budget limitation. We encourage all investigators at every professional level to submit their best ideas for advancing the state of knowledge about Barth Syndrome so that progress can be made in finding a specific treatment or a cure for this unusual mitochondrial disease. There are no geographical limitations to this funding.

Barth Syndrome (BTHS) is a serious X-linked genetic condition associated with cardiomyopathy, neutropenia, skeletal muscle weakness, exercise intolerance, growth delay, and diverse biochemical abnormalities (including defects in mitochondrial metabolism and phospholipid biosynthesis). Because many clinical and biochemical abnormalities of Barth Syndrome remain poorly understood, we are seeking proposals for both basic science and clinical research that may shed light on any aspect of the syndrome, with the ultimate objective of developing a specific treatment or a cure.

BSF is interested in providing financial assistance to investigators interested in exploring the field of BTHS science and/or clinical research. They anticipate that these funds might be useful as "seed grants" for the testing of initial hypotheses and the collection of preliminary data that can lead to successful long-term funding by the National Institutes of Health (NIH) and other major granting institutions around the world. In addition to those having prior research experience with BTHS, they encourage young investigators and experienced investigators that are new to the field of BTHS to submit proposals for funding.

BSF has a competitive grant process. Applications should be of 10–15 pages in length and must follow the instructions listed on the BSF website. In general terms, detailed information about the specific aims, significance, research design and methods, personnel, facilities, and budget will be required. A one-page, "letter of intent" is required for DEVELOPMENT grant applicants with a due date of September 1, 2013. The "letter of intent" is optional for IDEA grant applicants. We strongly encourage the submission of letters of

intent before the due date to allow ample time for review and feedback.

Completed applications (and/or "letters of intent") will be forwarded to the BSF Scientific and Medical Advisory Board (as well as to expert outside reviewers) for confidential evaluation. Response to the "letter of intent" will be communicated within 2 weeks of receipt. Based on the recommendations of the BSF Scientific and Medical Advisory Board, the BSF Board of Directors will make the final funding decisions about the grant applications. Please review BSF's "Grants Awarded" webpage for a listing of grants that BSF and its affiliates have awarded to date.

BSF anticipates awarding several IDEA and DEVELOPMENT grants each year. Funds will be available soon after the successful grant applicants have been notified in early March, 2014.

The deadline for submission of the completed research grant application is October 31, 2013, and grants will be awarded in early March, 2014. The deadline for the one-page "letter of intent," if applicable, is September 1, 2013.

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First Drug to Improve Heart Failure Mortality in Over a Decade

Coenzyme Q10 decreases all-cause mortality by half, according to the results of a multicentre randomised double-blind trial presented at the *Heart Failure 2013* congress. It is the first drug to improve heart failure mortality in over a decade and should be added to standard treatment, according to lead author Professor Svend Aage Mortensen (Copenhagen, Denmark).

Heart Failure 2013 was held May 25-28, 2013 in Lisbon, Portugal. It is the main annual meeting of the Heart Failure Association of the European Society of Cardiology.

Coenzyme Q10 (CoQ10) occurs naturally in the body and is essential to survival. CoQ10 works as an electron carrier in the mitochondria, the powerhouse of the cells,



Global Heart Network Foundation (GHN)

a global non-profit organization with a mission to connect people and organizations focused on the delivery of cardiovascular care across the Globe to increase access to care.

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www.globalheartnetwork.net

to produce energy and is also a powerful antioxidant. It is the only antioxidant that humans synthesise in the body.

CoQ10 levels are decreased in the heart muscle of patients with heart failure, with the deficiency becoming more pronounced as heart failure severity worsens. Statins are used to treat many patients with heart failure because they block the synthesis of cholesterol, but these drugs also block the synthesis of CoQ10, which further decreases levels in the body.

Double blind controlled trials have shown that CoQ10 improves symptoms, functional capacity and quality of life in patients with heart failure with no side effects. But until now, no trials have been statistically powered to address effects on survival.

The Q-SYMBIO study randomised 420 patients with severe heart failure (New York Heart Association (NYHA) Class III or IV) to CoQ10 or placebo and followed them for 2 years. The primary endpoint was time to first Major Adverse Cardiovascular Event (MACE) which included unplanned hospitalisation due to worsening of heart failure, cardiovascular death, urgent cardiac transplantation and mechanical circulatory support. Participating centres were in Denmark, Sweden, Austria, Slovakia, Poland, Hungary, India, Malaysia and Australia.

CoQ10 halved the risk of MACE, with 29 (14%) patients in the CoQ10 group reaching the primary endpoint compared to 55 (25%) patients in the placebo group (hazard ratio=2; p=0.003). CoQ10 also halved the risk of dying from all causes, which occurred in 18 (9%) patients in the CoQ10 group compared to 36 (17%) patients in the placebo group (hazard ratio=2.1; p=0.01).

CoQ10-treated patients had significantly lower cardiovascular mortality (p=0.02) and lower occurrence of hospitalisations for heart failure (p=0.05). There were fewer adverse events in the CoQ10 group compared to the placebo group (p=0.073).

Professor Mortensen said, "CoQ10 is the first medication to improve survival in chronic heart failure since ACE inhibitors and beta blockers more than a decade ago and should be added to standard heart failure therapy."

He added, "Other heart failure medications block rather than enhance cellular processes and may have side effects. Supplementation with CoQ10, which is a natural and safe substance, corrects a deficiency in the body and blocks the vicious metabolic cycle in chronic heart failure called the energy starved heart."

CoQ10 is present in food, including red meat, plants and fish, but levels are insufficient to impact on heart failure. CoQ10 is also sold over the counter as a food supplement, but Professor Mortensen said, "Food supplements can influence the effect of other medications including anticoagulants and patients should seek advice from their doctor before taking them."

Patients with ischaemic heart disease who use statins could also benefit from CoQ10 supplementation. Professor Mortensen said, "We have no controlled trials demonstrating that statin therapy plus CoQ10 improves mortality more than statins alone. But statins reduce CoQ10, and circulating CoQ10 prevents the oxidation of LDL effectively, so I think ischaemic patients should supplement statin therapy with CoQ10."

Letters to the Editor

Do you have comments or topics you would like to address, please send an email to: LTE@CCT.bz, and let us know if you would like your comment published or not.

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Do you have interesting research results, observations, human interest stories, reports of meetings, etc. to share?

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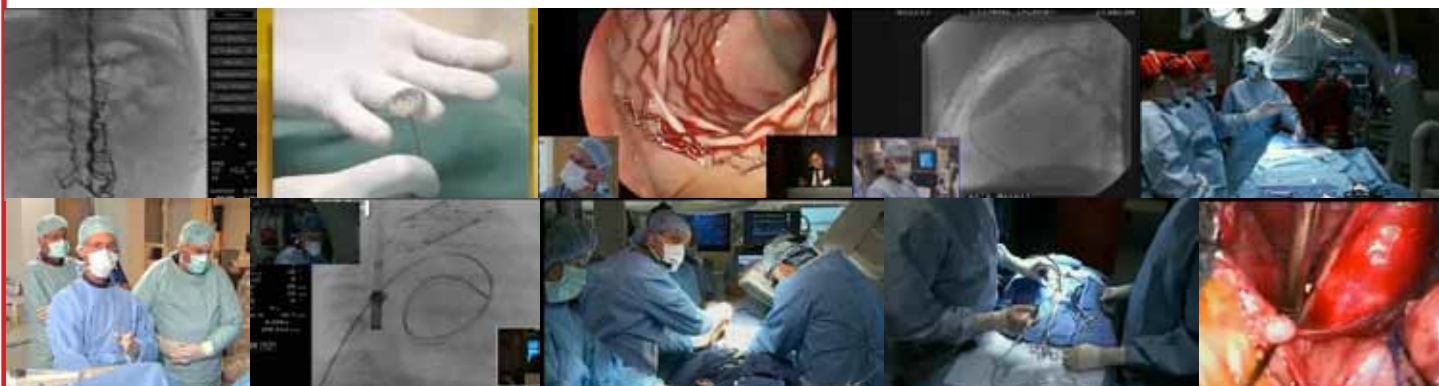
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