In recent years, epidemiologist Heather Boyd, PhD, senior researcher, Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark, has been investigating whether complications in pregnancy may lead to ischaemic heart disease in women in later life. Her recent article in *Circulation* is titled, “Pregnancy Loss and Later Risk of Atherosclerotic Disease,” for which her team followed >1 million women who were pregnant at least once between 1977 and 2008 and identified a cohort who had miscarriages, stillbirths, or live singleton births. They concluded that miscarriage and stillbirth were associated with a subsequent risk of myocardial infarction, cerebral infarction, and renovascular hypertension, consistent with either a shared aetiology or the initiation of pathological processes leading to atherosclerosis.

Dr Boyd says, “This is an instance where 2 processes that seem fairly unrelated might have a great deal to do with one another, which is exciting. This work could get us closer to a mechanism and to understanding the underlying genetic influences.”

“We may not be able to make the leap to treatment, but identification of women at risk of these events and the fact that we can say that miscarriage and stillbirth are risk factors for later myocardial infarction or cerebrovascular infarction are important. The question is ‘Is there something about repeated losses that could flip a switch in a woman and set up conditions for later disease or is there some common underlying factor? If we can show that repeated losses or stillbirths increase risk, then perhaps women with such histories need to be watched more closely for atherosclerotic disease later down the line.’”

“We Are Talking About Something That Is Not Just a Risk Factor for a Poor Pregnancy Outcome But Also an Important Risk Factor for Cardiovascular Disease in Women”

Dr Boyd’s research has 3 main strands. First, a number of her studies focus on complications in pregnancy, specifically preterm delivery and preeclampsia, looking at familial aggregation of events and whether that risk is passed on. She has recently received funding to look at the genetics of severe early preeclampsia in collaboration with Richa Saxena, PhD, of the Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA.

Dr Boyd’s second focus is on sudden unexpected death and cardiovascular disease epidemiology. Her group is currently investigating familial aggregation of myocardial infarction, the impact of family history on postmyocardial infarction prognosis, and whether familial recurrence can be prevented.

The third strand of her research falls at the intersection of the 2 fields and examines the potential link between complications of pregnancy and later ischaemic heart and cerebrovascular disease. Dr Boyd finds this strand most...
enjoyable. She explains, “This lets me combine 2 interests and investigate relevant problems at the same time.”

Important articles for Dr Boyd include those looking at the risk of cardiovascular disease in family members of young victims of sudden cardiac death and family history of premature death and risk of early onset cardiovascular disease. She says, “These 2 articles have the potential to change guidelines for how we deal with family members left behind after someone dies suddenly and unexpectedly.”

Dr Boyd is particularly proud of the Circulation article, as well as her work on preterm delivery in families and a 2005 article on Bayesian hierarchical modelling. “My article on Bayesian hierarchical modelling was complicated statistically. Being able to understand and apply those methods has enhanced my credibility among various statistical groups and opened doors for me,” she says.

Dr Boyd says her most important work, however, is her work on preterm delivery and preeclampsia, and the way outcomes run in families, alone and in combination with cardiovascular disease, “because of the sheer numbers of people affected by these conditions.”

She says, “The genetic work we are doing in preeclampsia is interesting because it is a fairly common condition that can become so severe that your only option is to deliver the baby regardless of whether it is anywhere near term. When you get to the fact that there might be a relationship between preeclampsia and ischaemic heart disease, we are talking about something that is not just a risk factor for a poor pregnancy outcome but also an important risk factor for cardiovascular disease in women. If we work out what the underlying mechanism is, we could have a much greater understanding of how both conditions develop.”

“The whole field of genome-wide association studies and deep sequencing has really shown us that it is not 1 gene for 1 organ system. Individual genes can be involved in multiple pathways and turn on processes that are involved in all sorts of things.”

“I am hoping that we will have some real breakthroughs in our projects on preeclampsia genetics and the overlap between preeclampsia and ischaemic heart disease.”

“We Ended Up in Denmark Where My Career Took a Sharp Turn, So I Am a Long Way From Where I Started”

Dr Boyd was born in Edmonton, Canada, where her mother Joanne Boyd worked as a public health nurse. Dr Boyd studied medical microbiology at the University of Alberta in Edmonton, graduating in 1996. She was awarded the Governor General’s Silver Medal (top University of Alberta undergraduate) and the Lieutenant Governor’s Gold Medal (top Faculty of Science undergraduate).

At the University of Alberta, Dr Boyd’s mentors were chemistry professor Karl Kopecky, PhD, who ensured that as a second-year undergraduate she “did not drown in a class full of graduate students,” while challenging her to compete academically with those same graduate students; and her honour’s degree supervisor Janet Robertson, PhD, professor of medical microbiology and immunology, who told Dr Boyd to do “whatever makes your heart leap, follow your heart.” Dr Boyd adds, “She was good at mentoring female students and ensuring that women stayed in the sciences.”

At this time, Dr Boyd was interested in infectious disease epidemiology, so she decided to study in the United States and was attracted by Emory University in Atlanta, GA, with its quest to become the “Harvard of the South.” She says, “It sounded like a great place to be particularly because I was interested in infectious disease epidemiology, and the Centers for Disease Control and Prevention was across the road.”

In Atlanta, Dr Boyd completed her dissertation on lymphatic filariasis in Haiti, a mosquito-borne parasite that causes elephantiasis and hydrocoele. Professor Dana Flanders, MD, DSc, chair of her dissertation committee, was a key influence. “He is an epidemiologist with an interest in epidemiological methods rather than any given subject area,” Dr Boyd explains. “He taught me about communicating difficult statistical and epidemiological concepts simply. He also made a point of ensuring I understood the methods I was applying and why and what the advantages of doing so might be.”

At the Centers for Disease Control and Prevention, David Addiss, MD, MPH, was Dr Boyd’s “introduction to compassionate research” and her focus on research that “makes a difference.” Dr Boyd says, “He dealt with the people with elephantiasis in Haiti as if they had worth as human beings, and he was not simply treating them as research subjects.”

After gaining her PhD, Dr Boyd began looking for work with her husband-to-be, biochemist Franta Hubálek. “He is Czech and prospective employers in the United States were daunted by the massive amounts of paperwork required to get him a work visa after 9/11. So we started looking elsewhere and ended up in Denmark, where my career took a sharp turn, so I am now a long way from where I started,” says Dr Boyd. They arrived in Copenhagen in the autumn of 2004, where Dr Boyd spent the first 2 years as “a green new PhD” in what was more or less a postdoc position. Dr Boyd says, “Denmark is known for its health registers, everything here is registered, so it is a wonderful place to do epidemiology, not necessarily just infectious disease epidemiology. I spent time learning about these registers because as someone who had never worked with them before, this was a whole new concept to me.”

Dr Boyd began to focus on the complications of pregnancy and then coupled that with cardiovascular epidemiology after hearing a talk on sudden unexpected death. “The idea that someone can just one day drop dead resonated, so together with the various complications of pregnancy, I started to look at sudden death. That took me into the cardiology field by the back door because a large proportion of these sudden unexpected deaths tend to have underlying cardiological causes.”

At around the same time, Dr Boyd received funding to conduct research into sudden unexpected death from a
cardiological point of view, after which Mattis Ranthe, MD, who is now beginning his specialty training in cardiology, joined her team as a PhD student.

“He is a dynamo, a rising star in his field,” Dr Boyd says. “He continuously throws off cardiological ideas and has good connections with Copenhagen University Hospital cardiology, so the whole thing snowballed.”

Another important colleague in Denmark has been her department chair, Professor Mads Melbye, MD, DMSc, who has helped Dr Boyd further her career, in the first place by hiring a newly graduated PhD researcher from North America, and then by mentoring her as she was promoted from being a junior researcher into her current position and opening up research opportunities.

Head statistician Jan Wohlfahrt, DMSc, has also been influential in Denmark. Dr Boyd explains, “He is infinitely patient and able to explain even the most difficult concepts simply and clearly. I look at him as a role model when it comes to teaching and supervising doctoral students. I also appreciate how he constantly challenges me to come up with the best possible study designs and to communicate my work as simply and clearly as possible.”

Dr Boyd and her husband, who works in insulin discovery, live just outside Copenhagen with their 2 young children, both of whom were born 6 to 7 weeks preterm, which she says gives “a little extra motivation to the research.”

Away from medicine and epidemiology, Dr Boyd’s interests include singing in a gospel choir, travel, hiking, cycling, and yoga. Dr Boyd says, “Denmark is a good place to live for juggling work and personal life if you have a family,” although she has not ruled out a return to her native Canada or a move elsewhere at some stage in their future.

References

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Awards: Foundation Coeur de la Tour Cardiovascular Research Prize

A Prize of 10000 Swiss Francs for the First Author of the Winning Article

Recipients of the Foundation Coeur de la Tour Cardiovascular Research Prize describe the article and their research that won the prize to Jennifer Taylor, BSc, MSc, MPhil.

The Foundation Coeur de la Tour Cardiovascular Research Prize is awarded annually to a clinical research project, published or accepted for publication in a peer-reviewed journal during the 2 previous years. The prize is 10000 Swiss Francs for the first author of the article. Candidates should be working in Switzerland in clinical cardiovascular medicine or be Swiss nationals working abroad for postgraduate training. The evaluation of submissions is made by a 5-member jury. The winner is invited to give a short oral presentation of their work during the foundation’s annual cardiac meeting.

An Analysis of Interventional Treatment for Symptomatic Chronic Coronary Artery Disease in Diabetic Patients >75 Years of Age

Raban V. Jeger, MD, staff interventional cardiologist, University Hospital Basel, Basel, Switzerland (head: Professor Stefan Osswald, MD), received the Coeur de la Tour Cardiovascular Research Prize in 2006 for a follow-up article of the Trial of Invasive versus Medical Therapy in Elderly Patients with Chronic Symptomatic Coronary Artery Disease (TIME) published in 2001 in the Lancet. TIME investigated interventional treatment for symptomatic chronic coronary artery disease in patients >75 years of age. Patients who had angina pectoris Canadian Cardiovascular Society class II or more despite at least 2 anti-anginal drugs were randomised to either an interventional treatment including coronary angiography and revascularisation or a conservative treatment with optimised medical therapy. The study found a clear benefit of percutaneous coronary intervention compared with anti-ischaemic treatment in terms of symptom relief and quality of life.

Using long-term follow-up data, an analysis of the important subgroup of diabetic patients was published in 2005 and found that diabetic patients have a worse outcome than their nondiabetic counterparts but profit similarly from interventional treatment. Dr Jeger says, “The Coeur de la Tour Cardiovascular Research Prize 2006 recognised the important contribution of the TIME investigators to clinical research in the field of interventional cardiology, specifically for the results of the analysis of the high-risk subgroup of diabetic patients.”

He adds, “The TIME study was the first of a series of important studies led by the University Hospital of Basel.” These have included the B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study published in 2004, the Basel Stent Kosten Effektivitäts Trial (BASKET) published in 2005, the Trial of Intensified Versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF), the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study published in 2009, and the BASKET-Perspective Validation Examination (BASKET-PROVE) published in 2010.

Reference

Evaluating Mechanical Dyssynchrony Using Standard Pulsed-Waved Doppler and M-Mode Echocardiography

Haran Burri, MD, staff physician, Electrophysiology Unit, Cardiology Service, University Hospital of Geneva, Geneva, Switzerland, received the prize in 2008 for an article evaluating 44 patients with a left ventricular ejection fraction <0.35 for mechanical dyssynchrony using standard pulsed-wave Doppler and M-mode echocardiography. Echocardiographic measurement of dyssynchrony has been strongly advocated by some authors for patient selection for cardiac resynchronization therapy. A variety of different measurements of dysynchrony have been proposed, but whether these techniques yield concordant results was unknown. Results were compared using pulsed-wave tissue Doppler imaging. Agreement for diagnosing inter- and intraventricular dysynchrony was found to be low ($\kappa <0.33$ for all comparisons). Also, reproducibility of tissue Doppler imaging measurements was poor, making them unsuitable for clinical use.
Determining the Incidence and Causes of Defibrillator Lead Malfunction of Implantable Cardioverter-Defibrillators Necessitating Surgical Revision and Evaluating Management

Jens Eckstein, MD, PhD, senior consultant, Department of Medicine, University Hospital Basel, Basel, Switzerland, received the prize in 2009 for an article that described the incidence and causes of lead malfunction necessitating surgical revision and evaluating 2 approaches to treat lead malfunction.

Defibrillator lead malfunction is a potential long-term complication in patients who have an implantable cardioverter-defibrillator (ICD). The investigators recorded the types and causes of lead malfunction among 1317 consecutive patients who had an ICD implanted at 3 European centres between 1993 and 2004. If the integrity of the high-voltage part of the lead could be ascertained, an additional pace/sense lead was implanted. Otherwise, the patients received a new ICD lead.

Of the 1317 patients, 38 experienced lead malfunction requiring surgical revision and 315 died during a median follow-up of 6.4 years. At 5 years, the cumulative incidence was 2.5% (95% confidence interval, 1.5 to 3.6). Lead malfunction resulted in inappropriate ICD therapies in 76% of the cases. Implantation of a pace/sense lead was feasible in 63%. Both lead revision strategies were similar with regard to lead malfunction recurrence (p=0.8). However, the cumulative incidence of recurrence was high (20% at 5 years; 95% confidence interval, 1.7 to 37.7).

Dr Eckstein says, “Lead malfunction necessitating surgical revision becomes a clinically relevant problem in 2.5% of ICD recipients within 5 years. In selected cases, simple implantation of an additional pace/sense lead is feasible. Regardless of the chosen approach, the incidence of recurrent ICD lead-related problems after lead revision is 8-fold higher in this population.”

At present Dr Eckstein focuses on clinical atrial fibrillation research after spending 4 years on basic research in the research group of Maurits Allessie, MD, PhD (see http://circ.ahajournals.org/124/7/137) and Ulrich Schotten in Maastricht, the Netherlands. The only way to diagnose atrial fibrillation is to document it with an electrocardiogram when the patient presents with the arrhythmia, but in sinus rhythm it is not possible to tell whether an individual has paroxysmal atrial fibrillation. “This information is relevant because it would result in the recommendation for anticoagulation therapy in the majority of these individuals to prevent cardioembolic stroke and heart failure,” says Dr Eckstein. “We work on techniques to identify individuals in sinus rhythm who have paroxysmal atrial fibrillation.”

Demonstrating That Patients Included in Prophylactic Implantable Cardioverter-Defibrillator Trials Represent a Minority of the Patients at Risk of Sudden Cardiac Death

Patrizio Pascale, MD, junior attending physician in electrophysiology and pacing, Service of Cardiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, received the prize in 2010 for an article demonstrating that patients included in prophylactic ICD trials represent a minority of patients at risk of sudden cardiac death.

Estimates of left ventricular ejection fraction in patients with sudden cardiac death related to coronary artery disease have rarely been reported despite being the basis for determining patients’ eligibility for a prophylactic defibrillator. Dr Pascale therefore determined the extent and distribution of reduced left ventricular ejection fraction and evaluated angiographic findings in patients with ventricular arrhythmia related to coronary artery disease.

Dr Pascale says, “Current recommendations are largely based on these trials, so our findings challenge the adequacy of the actual primary prevention strategy. While previous studies focused on the ‘quantitative’ issue of previous myocardial infarction characterisation, we demonstrated an unexpected highly significant relation between old inferior myocardial infarction and substrate-related arrhythmias.”

Dr Pascale’s current research focuses on the understanding of atrial fibrillation dynamics and organisation with the aim of identifying the most critically vulnerable
ablation targets in persistent atrial fibrillation. Frequency-based analysis of intracardiac recordings is performed to identify the sources that maintain atrial fibrillation.

Reference

Explaining the Pathogenesis of Very Late Stent Thrombosis
Stéphane Cook, MD, FESC, professor in sciences and cardiology and head of Cardiology, Fribourg University and Hospital, Fribourg, Switzerland, received the prize in 2012 for an article identifying structural changes at the stent level that help explain the pathogenesis of very late stent thrombosis (ie, occurring after >1 year).

Professor Cook and his colleagues compared the intravascular ultrasound findings in 13 patients presenting acutely with very late stent thrombosis with intravascular ultrasound findings obtained 8 months after drug-eluting stent implantation in 144 control patients, who did not experience stent thrombosis for >2 years. They observed a “positive” or “outward” remodelling of the external elastic membrane and a high prevalence of incomplete stent apposition in patients with very late stent thrombosis compared with controls.1 Professor Cook says, “These morphological changes could be explained by a chronic inflammatory response at the vicinity of the stent struts, leading to endothelial dysfunction, delayed arterial healing, and positive vascular remodeling. Autopsy studies of patients with very late stent thrombosis showed extensive vasculitis due to hypersensitivity reactions.”

The investigators then tried to correlate intravascular ultrasound findings with the results of histopathological analysis of thrombi harvested from the occluded coronary artery at the time of very late stent thrombosis. Signs of acute and chronic inflammation were observed in the stented segments.2 Eosinophilic infiltrates were more common in patients with very late stent thrombosis compared with controls, and the number of eosinophils correlated with the intravascular ultrasound findings: the more eosinophils found in the thrombus, the more outwards vessel remodelling and incomplete stent apposition.

On reviewing the intravascular ultrasound findings in 194 patients at 8 months, Professor Cook and his team found evidence of incomplete stent apposition among 37 patients with 39 lesions (18%) but no evidence among 157 patients with 182 lesions. After 4 years of prospective clinical follow-up, incomplete stent apposition was associated with an increased rate of myocardial infarction due to an exaggerated rate of very late stent thrombosis.3

Professor Cook says, “Taken together, these data underline that drug-eluting stents with durable materials might induce delayed drug hypersensitivity reactions that could be demonstrated with intravascular ultrasound before stent thrombosis happens.”

References

Jennifer Taylor is a freelance medical journalist.