A recent article in *Circulation* has confirmed current American College of Cardiology/American Heart Association guidelines that thyroid function should be assessed in patients with heart failure and contributes to a better interpretation of thyroid stimulating hormone levels. Previously, prospective data on the association between subclinical thyroid dysfunction and heart failure events were limited, so the guidelines do not specify the impact of different thyroid stimulating hormone levels. The last author of the article, Nicolas Rodondi, MD, MAS, professor of medicine and head of ambulatory care, Department of General Internal Medicine, Inselspital, Bern University Hospital, Bern, Switzerland, says, “What we found was that risks of heart failure events were increased with both higher and lower thyroid stimulating hormone levels. Our study involved >25 000 participants, so we were able to identify subgroups at risk and we confirmed the recommendation in many guidelines that patients with heart failure should be assessed for thyroid dysfunction. We also identified the groups at highest risk of heart failure in relation to thyroid dysfunction. From 6 prospective cohorts, we were able to understand the relationship between thyroid dysfunction and heart failure.”

Professor Rodondi has brought together the disparate data on the link between thyroid dysfunction and cardiovascular health by collecting individual participant data in addition to usual study-level meta-analysis from all cohort studies on the subject from across the world in recent years. He has also facilitated collaboration between experts in a range of disciplines to advance understanding of the subject.

A next step is the European Union Framework Programme 7-funded Thyroid Hormone Replacement for Subclinical Hypothyroidism Trial (TRUST) trial of 3000 older adults to examine the effects of thyroid hormone replacement for untreated older adults with subclinical hypothyroidism and endeavour to identify the subgroups that may benefit from treatment. Professor Rodondi is the principal investigator for Switzerland, together with Professors Jacobijn Gussekloo, MD, PhD, Leiden University Medical Center, Leiden, the Netherlands, and Rudi Westendorp, MD, PhD, Leyden Academy on Vitality and Ageing, Leiden; Professor David Stott, MD, MBChB, FRCP (coordinator of the trial), Glasgow University, Glasgow, Scotland; and Patricia Kearney, MBBCh, MRCPI, MPH, PhD, University College Cork, Cork, Republic of Ireland. Professor Rodondi says, “The goal of this trial is to address the relationship between thyroid dysfunction and multiple systems in older adults. In observational studies, thyroid dysfunction has been seen to impact not only the heart but also cognition, muscular function, and quality of life. TRUST will be the first trial to assess the clinical impact of treating thyroid dysfunction. All previous trials have assessed surrogate markers instead.”

**Spotlight: Nicolas Rodondi, MD, MAS**

Investigating the Relationships between Thyroid Dysfunction and Cardiovascular Disease, and Testing the Impact of Treatment of Thyroid Dysfunction on Clinical Outcomes

Nicolas Rodondi, MD, MAS, professor of medicine and head of ambulatory care, Department of General Internal Medicine, Inselspital, Bern University Hospital, Bern, Switzerland, talks to Mark Nicholls.

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**Funding: Fondazione “Per il Tuo Cuore” (Heart Care Foundation) Scholarships**

Recipients of Fondazione “Per il Tuo Cuore” scholarships describe their research.
TRUST is working in close collaboration with other trialists assessing the same issue in a unique international effort to solve the controversial clinical issue of treating thyroid dysfunction, which has been mentioned in all guidelines over many years, without any large-scale formal testing. It coincides with research by a group in the Netherlands led by Simon Mooijart, MD, PhD, director of the Institute for Evidence-based Medicine in Old Age, Leiden, to investigate the impact of treating thyroid dysfunction in 400 very elderly subjects. For several years, Professor Rodondi has also participated in a US consortium led by Professor Doug Bauer, MD, University of California, San Francisco, CA, and funded by a planning grant from the National Institute of Ageing, which hopes to launch a large randomised, controlled trial of thyroid dysfunction, with a similar protocol as TRUST. These 3 groups have now agreed to make their protocols identical to enable pooling of their data and allow reliable analysis of important subgroups to collaboratively forward research in this area. A biobank will also be developed to enhance research in this field, with future studies looking at biomarkers and the impact of treating thyroid dysfunction on depression and anaemia.

“We Decided to Clarify the Relationship between Thyroid Dysfunction and Cardiovascular Disease”

Professor Rodondi developed his interest in cardiovascular disease as a medical student at the University of Lausanne, Switzerland. He says, “I found it attractive not only to cure disease but also to prevent it. The first large studies on statins were published when I was a student and it seemed to me that a new field was opening up to treat certain cardiovascular risk factors and have a large impact on public health, although a number of controversies clearly demonstrated the need for additional research in this field.”

After graduating in medicine in 1997, Professor Rodondi trained in internal medicine at the University Hospital of Lausanne. He then spent 2 years as a clinical research scholar in the Department of Medicine, University of California, San Francisco, where he received “excellent training in clinical epidemiology and patient-oriented clinical research” from Professor Bauer, an expert in osteoporosis, thyroid dysfunction, and clinical trials. Professor Rodondi’s main interest remained cardiovascular disease prevention, and as their collaboration progressed they discovered a common interest in thyroid dysfunction. Professor Rodondi says, “Professor Bauer was interested in risk factors for osteoporosis and the relationship between thyroid dysfunction and osteoporosis. We decided to explore the field of thyroid disease and looked at the potential relationship between thyroid dysfunction and cardiovascular disease. At the time, it was a field with limited data. After that I focused most of my research on this area.”

This experience significantly influenced the direction of Professor Rodondi’s future research, facilitated connections with experts and studies in the United States, and underlined his interest in cardiovascular disease risk factors and prevention of cardiovascular disease. It also gave him the opportunity to attend a 2-week American Heart Association course on epidemiology and cardiovascular prevention at Lake Tahoe, Sierra Nevada.

Professor Rodondi returned to Lausanne to the Department of Ambulatory Care in 2005. He was appointed as head of ambulatory care in the Department of General Internal Medicine in Bern in 2011. In this role, he provides care for inpatients and outpatients, teaches residents and general practitioners, and oversees several research projects. Professor Rodondi says, “We have a strong research network, with many experts working on patient-oriented clinical research. Because I am also working in the clinic and teaching, we can assess a problem in the clinic and formulate a clinical study to address it on the same day. I think patient-oriented research is attractive for young researchers because you can combine what you see in the daily clinic with research questions. I like to teach evidence-based medicine, and our department at Bern has the highest rating for our teaching and training in internal medicine among university hospitals in Switzerland.” Professor Rodondi is grateful for the support he has received from Professor Drahomir Aujesky, MD, MSc, who is now head of his department at the University of Bern.

“Patient-Oriented Clinical Research Can Be Very Rewarding, Especially When You Can Investigate the Gaps in Knowledge That Become Evident During Clinical Work”

One of Professor Rodondi’s most impactful articles investigated subclinical hypothyroidism and the risk of coronary heart disease and mortality.² He comments that, although
thyroid hormones have many effects on heart function and genes, and a metabolic impact such as elevating cholesterol and causing coagulation problems, data on the subject are conflicting. Previous studies had suggested that the impact of subclinical hypothyroidism could vary according to age group and level of thyroid dysfunction. Professor Rodondi’s most cited article to date examined subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. He says, “It is a highly cited article because it was one of the first prospective evaluations of the risk of thyroid dysfunction looking at clinical events. Most previous articles were only cross-sectional analyses.”

Professor Rodondi’s other important articles include one testing the impact of carotid plaque screening and another investigating screening with electrocardiograms.

An article that had a significant impact on Professor Rodondi’s work and the way he thinks was published in 2004 by Martin Surks, MD, and his research group. Professor Rodondi says, “This extensive review on thyroid dysfunction identified the gaps in our knowledge, and many of my future articles would try to fill in these gaps.”

Professor Rodondi’s research is supported by the European Grant Euresearch FP7-HEALTH-2011, Specific Programme “Cooperation”—Theme “Health” Investigator-Driven Clinical Trials for Therapeutic Interventions in Elderly Populations (Proposal No: 278148-2) and the Swiss National Science Foundation (SNSF 320030-138267).

Professor Rodondi advises people entering cardiovascular research to “Get involved early on, doing 1 or 2 years of research training.” He adds, “It is important that we offer research training positions to motivate young people. Patient-oriented clinical research can be rewarding, especially when you can investigate the gaps in knowledge that become evident during clinical work.”

Professor Rodondi was born in Lausanne and still lives in the city in the French-speaking part of Switzerland, commuting by train every day to Bern, which is in the German-speaking part of the country. “It offers a language challenge every day,” he says. Professor Rodondi is married to Frederique, and they have 4 children, aged 4 to 11 years, who all play the violin. Away from medicine, he enjoys music, including the music created by the family, reading, and hiking in the Swiss Alps.

In the future, Professor Rodondi plans to focus on the TRUST trial and his collaborations with the US and Dutch teams looking at the multisystem impact of thyroid dysfunction in older people. He says, “I think our TRUST trial and the partner studies are going to help clarify whether treatment is effective and safe. We will be able to identify the subgroups that will benefit from treatment. I am proud to be involved in international collaborations where we can pull data from 5 continents and involve people with different languages and expertise.”
The Fondazione “Per il Tuo Cuore” (Heart Care Foundation) in Florence, Italy, offers scholarships to graduates in medicine and surgery <40 years of age who have a particular interest in clinical research in cardiovascular care. The foundation’s president is Professor Attilio Maseri, MD (see http://circ.ahajournals.org/content/119/1/f1).

Marco Magnoni, MD, fellow in cardiology and clinical researcher, Fondazione “Per il Tuo Cuore” (Heart Care Foundation), Florence

Dr Magnoni was awarded a scholarship in 2009 to undertake an Italian multicentre innovative clinical research project. The study has been supported by the Heart Care Foundation and involves selected centres of the L’Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO; Italian Association of Hospital Cardiologists) network.

The innovative aspect of this clinical research project is to focus on individuals who deviate most from the traditionally accepted paradigm based on the close correlation between severity and extent of coronary atherosclerosis and traditional risk factors. The subjects are individuals without coronary atherosclerosis in spite of multiple risk factors and individuals with diffuse atherosclerosis of the coronary arteries in the presence of a low risk factor profile. “These are both ‘outliers’ with respect to the established paradigm,” says Dr Magnoni. “The aim of the project is to search for unknown protective factors in the first group and for new atherogenic factors in the second group to develop a novel working hypothesis to be tested.”

The scholarship funding enabled Dr Magnoni to contribute to the planning and design of a clinical study of individuals at the opposite extremes of the traditional risk factor profile and coronary atherosclerosis documented by multidetector computed tomography angiography—the Coronary Atherosclerosis in Outlier Subjects: Protective and Individual Risk factor Evaluation (CAPIRE) study. This multicentre, prospective, observational study of individuals without evidence of ischaemic heart disease, with a cross-sectional comparison and a 5-year follow-up involves 11 cardiovascular centres.

Dr Magnoni is the scientific coordinator of the study and a member of the steering committee. The chair is Professor Maseri, while the ANMCO Research Centre directed by Professor Aldo P. Maggioni, MD (see http://circ.ahajournals.org/content/120/2/f7) is responsible for organisational support. Daniele Andreini, MD, Centro Cardiologico Monzino, Milan, Italy, manages the multidetector computed tomography core lab, and Roberto Latini, MD, and Serge Masson, PhD, Mario Negri Pharmaceutical Institute, Milan, Italy, coordinate the dedicated biobank, collecting the blood samples of each subject for biomarker assays. The first subject was enrolled in January 2011. Currently, almost 400 subjects have been selected, of whom 84 have normal coronary arteries but multiple risk factors and 73 have diffuse coronary atherosclerosis but 0 or 1 risk factor, and the recruitment will be concluded in 2013.

Previously, Dr Magnoni’s research has mainly focused on acute coronary syndrome pathophysiology and the development of a novel method for assessing atherosclerotic plaque neovascularisation with contrast-enhanced ultrasound. Dr Magnoni concludes, “The CAPIRE study is an exciting challenge for my career in clinical research, providing me with the opportunity to plan and manage complex clinical studies, to work with brilliant scientists, and to investigate individual biodiversity in the ‘one-size-fits-all’ era. Furthermore,” he adds, “Attilio Maseri’s teaching about the importance of clinical observation has stimulated my interest for unusual clinical cases.”

Margherita M. Calcagnino, MD, fellow in cardiology and clinical investigator at Fondazione “Per il Tuo Cuore” (Heart Care Foundation), Florence, and PhD student, University of Pavia, Pavia, Italy

Dr Calcagnino was awarded a scholarship by the Fondazione “Per il Tuo Cuore” to undertake an innovative clinical research project that involves a number of centres of the ANMCO network across Italy. She says, “The new concept of this research project is to focus on patients who deviate most from the expected clinical path (outliers) and develop an unexpected favourable evolution despite severe left ventricular systolic dysfunction during hospitalisation for
Giorgio Napolitano. Photograph courtesy of Dr Calcagnino.

award ceremony before the President of the Republic of Italy, Dr Calcagnino at the Fondazione “Per il Tuo Cuore” scholarship

STEMI severe left ventricular systolic dysfunction.

clinical study that investigates outlier patients with post-

and planning of a prospective, observational, multicentre

Professors Maseri and Maggioni to contribute to the design

ship funding enabled Dr Calcagnino, in collaboration with

ST-elevation myocardial infarction (STEMI), and compare

them to matched cases with poor outcomes.” The scholar-

ship funding enabled Dr Calcagnino, in collaboration with

Francesco Orso, MD, and under the leadership of

them to matched cases with poor outcomes.” The scholar-

The study will be a substudy of the Stem Cells

Mobilisation in Acute Myocardial Infarction Outcome (STEM-AMI OUTCOME) trial, conducted by Felice

Achilli, MD, and Giulio Pompilio, MD, PhD. This phase

III, randomised, controlled, single-blind, multicentre study

will enroll 1530 patients (1:1 randomisation) to granulo-

cyte colony-stimulating factor therapy or placebo. The Out-

liers Substudy will select those patients enrolled in the

STEM-AMI OUTCOME trial who deviate most from the

expected results to try and find an explanation for this

behaviour. Phenotypically homogenous patients at the extreme

ends of the spectrum will be included in a prospective fol-

low-up programme and studied by monitoring their clini-

cal, instrumental, and biological characteristics, focusing

on those who develop an unexpected favorable evolution.

“The aim of our substudy is to concentrate on individ-

ual biodiversity and identify biomolecular markers and

mechanisms of long-term unexpected favourable evolution in a population at high risk of adverse outcome for left ven-

tricular systolic dysfunction,” says Dr Calcagnino. “Indeed

the identification of such indicators might lead to the dis-

covery of unknown paths of myocardial repair, which may provide opportunities for yet unknown forms of therapy.”

Previously, Dr Calcagnino investigated biomarkers and

genetics in coronary artery disease during her cardiology

specialty training. During her post-residency period at The

Heart Hospital, University College, London, England, her

research focused on cardiomyopathies. She says, “Thanks to the ‘Per il Tuo Cuore’ scholarship, our STEM-AMI OUTCOME Outliers Substudy represents a major step up in my career, enabling me to take part in the development of a breakthrough research approach focused on outliers, who are usually marginalised by mainstream medical research.”

Dr Calcagnino at the Fondazione “Per il Tuo Cuore” scholarship award ceremony before the President of the Republic of Italy, Giorgio Napolitano. Photograph courtesy of Dr Calcagnino.

Dr Ammirati (right) with Dr Palini, director of the flow cytometry unit, San Raffaele Scientific Institute, at work in the lab on July 9, 2012. Photograph courtesy of Dr Ammirati.

Enrico Ammirati, MD, postgraduate in cardiology and scientist physician, San Raffaele Vita-Salute University and Niguarda Ca’ Granda Hospital, Milan, Italy

Dr Ammirati received a 1-year “Per il Tuo Cuore” scholar-

ship with the support of Professor Maseri. During this time, he finalised experiments to study the role of the T-

lymphocyte and cytokine response in atherosclerosis and their interactions with lipoproteins. He collaborated with experts in flow cytometry (Alessio Palini, PhD, San Raffaele Scientific Institute, Milan), lipid metabolism (Guiseppe D. Norata, PhD, Università di Milano, Milan), and systems biology (Carlo V. Cannistraci, PhD, University of California, San Diego, CA). He found that circulating effector memory T cells are associated with increased atherosclerosis and coronary artery disease in humans and animal models. The presence of increased lev-

els of effector memory T cells suggest the possibility of targeting plaque chemotaxis and/or antigen encountering as emerging antiatherosclerotic strategies in addition to cardiovascular risk factor control.

“My interests in the immune response and clinical car-

diology led to my work as a clinician involved in the heart transplantation programme at Niguarda Ca’ Granda Hospital, Milan, directed by Maria Frigerio, MD,” says Dr Ammirati. “My professional career reflects the philosophy of the ‘renaissance of clinical observation’ proposed by my mentor Professor Maseri. I believe that from clinical obser-

vations, one can generate the incentive to search for new causal components of specific cardiovascular disease.”

During the scholarship, Dr Ammirati also planned a cli-

nical research study with Francesco Prati, MD, of San Gio-

vanni Hospital, Rome, Italy, based on optical coherence

tomography to better characterise the inner structure of the coronary tree of patients at the extremes of the clinical spectrum of coronary artery disease. They will compare contrasting groups of patients (one group with recurrent myocardial infarction, the other group with long-lasting and diffuse coronary atherosclerosis without previous acute events) to discriminate causal components of plaque instability and stability.

During his scholarship, Dr Ammirati applied for a grant from the Italian Ministry of Health as principal investigator...
with the supervision of Professor Paolo G. Camici, MD (see http://circ.ahajournals.org/content/117/3/F13), Vita-Salute San Raffaele University, Milan. “I ranked third, and I received a grant for a 3-year project (project code: GR-2009-1608780), allowing me to further develop my current research at the San Raffaele Scientific Institute,” says Dr Ammirati. “The aim of this project is to investigate the clinical value of assessing carotid plaque inflammation by positron emission tomography/computerised tomography with 11C-PK11195 (a marker of activated macrophages) to noninvasively identify asymptomatic patients at increased risk of ischaemic stroke.”

Dr Ammirati concludes, “The 1-year ‘Per il Tuo Cuore’ scholarship gave me the opportunity to continue experimental work, meet brilliant scientists, and further develop my future through writing grants to finance my research.”

Bruno Merlanti, MD, fellow in cardiac surgery and clinical researcher, Fondazione “Per il Tuo Cuore” (Heart Care Foundation), Florence

Dr Merlanti, a fellow in cardiac surgery in the cardiac surgery department directed by Luigi Martinelli, MD, Niguarda Ca’ Granda Hospital, Milan, has collaborated with the Heart Care Foundation ANMCO Centro Studi in the GISSI Outliers Programme since 2009. “The programme is a new way to conduct clinical research,” explains Dr Merlanti. “The main purpose of outlier studies is to identify patients whose clinical behaviour is at the extreme opposite ends of the expected average. As a surgical trainee, I focused on a protocol that involved cardiologists and cardiac surgeons in the study of outlier patients.”

Dr Merlanti’s department in Niguarda has been studying the bicuspid aortic valve for a decade. This condition is generally associated with an increased risk of valvular dysfunction (aortic stenosis, aortic regurgitation, endocarditis) and vascular disease (aneurysm, aortic dissection). “From the literature, we know that there is a grade of bicuspid aortic valve inheritance in families, and specific tissue degenerations are bicuspid aortic valve-related,” says Dr Merlanti. “However, only a few patients with bicuspid aortic valve develop 1 or more of these diseases, and often with different phenotypes.”

In collaboration with the Heart Care Foundation, Dr Merlanti contributed to the design of the GISSI Outliers VAR study, an investigation of patients with bicuspid aortic valve requiring Valve and/or Aortic Repair, correlating surgical and echo distinctive features with histological and genetic findings in phenotypically homogenous outlier cases. The protocol involves 13 cardiac surgery and cardiology departments in Italy. All patients are enrolled according to specific bicuspid aortic valve phenotypes eligible for surgery. Each patient has a transoesophageal echo before the surgical session, and tissue samples are collected during surgery. In addition, genetic tests will be performed to assess bicuspid aortic valve-related gene expression. Transthoracic echo will also be performed in first-degree relatives to quantify bicuspid aortic valve prevalence in families, and, if confirmed, a blood sample will be collected for genetics. All the collected data will be analysed by core labs, and all biosamples will be stored in a biobank at the Mario Negri Pharmacological Institute, Milan. The aim is to identify markers and predictors of aortic wall disease and bicuspid aortic valve function evolution to evaluate whether a bicuspid aortic valve phenotype is more likely to be at high risk for valvular or vascular degeneration.

Dr Merlanti says, “As a young clinical researcher, it is a great pleasure to have the opportunity to work under the supervision of Professor Maseri, the chair of the study, Luigi Martinelli, MD (co-chair), and Professor Gaetano Thiene, MD (see http://circ.ahajournals.org/content/118/19/f109; the pathology core lab), and to collaborate with many Italian cardiac surgeons.” He concludes, “This study is a revolutionary way to perform clinical research: first, it has been innovatively designed to focus on small groups of ‘phenotypically homogenous’ patients at extreme opposite ends of the average; and second, it involves cardiac surgeons, giving me a real and innovative new perspective of study.”

Jennifer Taylor is a freelance medical journalist.