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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.

A recent article in *Circulation*¹ 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 relationship 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."

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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.

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The principal investigators (experts in ageing, thyroid problems, clinical epidemiology, and vascular disease) from around Europe of the EU FP7-funded TRUST project at the kick-off meeting in Glasgow. From left to right: Dr Kearney, Professor Rodondi, Professor Gussekloo, Professor Stott, and Professor Westendorp. Photograph courtesy of Professor Rodondi.

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, 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.³ 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 screening⁴ and another investigating screening with electrocardiograms.⁵

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.⁶ 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."

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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."



World map depicting the International Thyroid Studies Collaboration, which is coordinated by Professor Rodondi's group, who have collected data from all studies worldwide on the relationship between thyroid dysfunction and cardiovascular disease. Their analysis of individual participant data from >60 000 patients is the largest study to date on the relationship between thyroid dysfunction and cardiovascular disease. "We had experts from several different fields—cardiology, endocrinology, clinical epidemiology, biostatistics, and geriatrics—which gave us a large expert group and a very interesting international collaboration," says Professor Rodondi. Illustration courtesy of Professor Rodondi.

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Contact details for Professor Rodondi:

Department of General Internal Medicine, Inselspital, University of Bern, Switzerland. Tel: + 41 31 632 41 63. Fax: + 41 31 632 88 85. E-mail: Nicolas.Rodondi@insel.ch

Mark Nicholls is a freelance medical journalist.