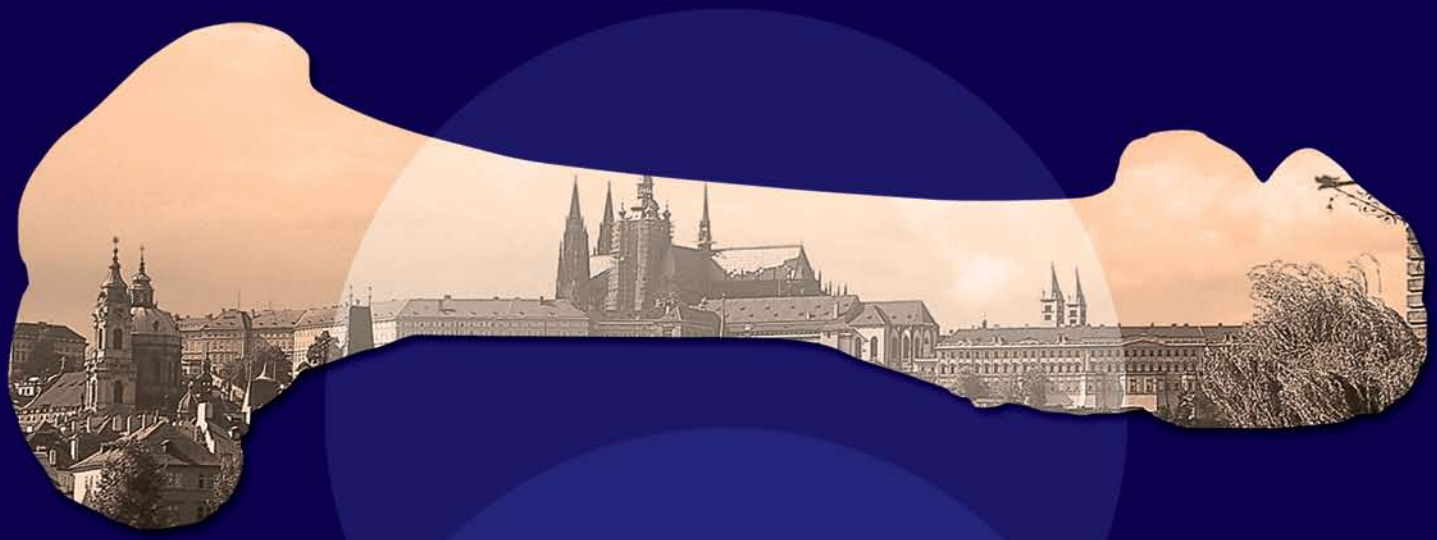
4TH EUROPEAN OSTEOPOROSIS SUMMIT

CENTRAL EASTERN EUROPE

CONGRESS BOOK



3. – 5. DECEMBER 2010, PRAGUE, CZECH REPUBLIC

THE MEETING IS ORGANIZED BY SMOS AND AUSTRIAN SOCIETY OF OSTEOPOROSIS

AUSTRIAN SOCIETY
OF OSTEOPOROSIS

SPONSORED BY UNRESTRICTED EDUCATION GRANT FROM AMGEN gsk GlaxoSmithKline

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CONTENTS

WELCOME LETTER

Dear friends and colleagues,

Let us welcome you to Czech Republic, to Prague, and especially to the **4th Central European Summit on Osteoporosis**. Meetings of physicians and scientists in osteology of our countries have become a tradition, take place in all our countries and attract enthusiastic people. Osteology is very important discipline in clinical medicine, aimed at specialists from endocrinology, rheumatology, gynaecology, orthopaedics, internal medicine and many other medical fields. It is an interesting field, rapidly evolving, and brings better care for our patients and more knowledge to us.

This year we decided to change the form of the meeting a little bit. As you can see from the Program, this year's Summit is not focused on the diagnostics (except for the Opening Plenary lecture). It is focused on the therapy and its benefit and also some drawbacks and risks. We have asked top-level scientists to prepare *pro* and *contra* lectures about the main therapy groups. And even more – one of the most interesting lectures is focused on preclinical observation and development of new drugs and will be given by our honorary guest Serge Ferrari.

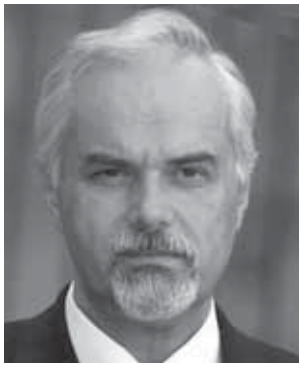
The hot topic of nowadays is (again) vitamin D. Its role is definitely important not only in osteoporosis and other metabolic bone diseases. But in osteology there are still plenty of saunsolved problems around Vitamin D. Starting from the uncertainty what and how to measure, over dosing in primary osteoporosis and target values, to the role and importance of vitamin D in secondary osteoporosis and other metabolic diseases of bones vitamin D is discussed and commented.

We are sure that everyone will find plenty of news in science; but our role is also in declaring our strategy and preparing guidelines. Using the Swiss' experience as a model we would like to discuss the suitable philosophy of National Guidelines in Diagnostics and Therapy, and share the experiences between our countries.

We hope that Prague will give you high science, plenty of news, and also good spirits and social atmosphere in one of the most beautiful cities in the world.

Enjoy your stay here !

Professor Heinrich Resch
President of ÖGEKM

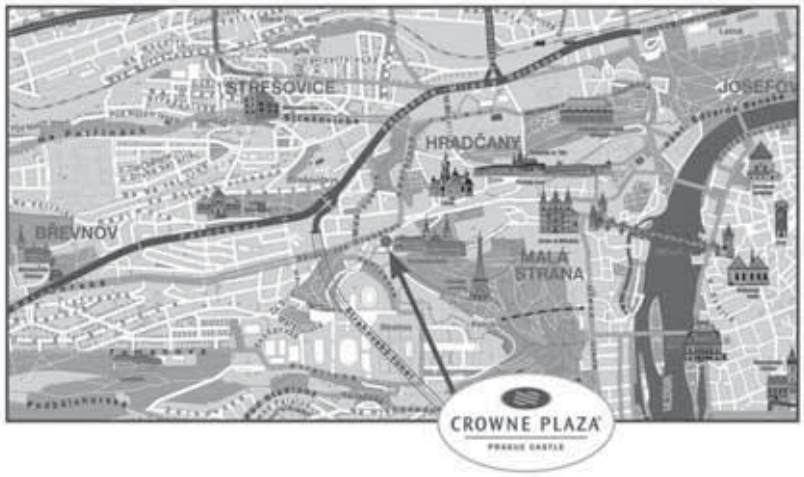


Professor Vladimir Palicka
President of SMOS

GENERAL INFORMATION

VENUE

Hotel Crowne Plaza Prague Castle
Strahovská 128
118 00 Prague 1
Czech Republic
www.crowneplaza.com



REGISTRATION DESK WILL BE OPEN:

Friday, Dec 3 – 11.00 – 20.00
Saturday, Dec 4 – 08.00 – 18.00
Sunday, Dec 5 – 08.00 – 13.00

CEE SUMMIT SECRETARIAT

Congress Business Travel
Lidická 43/66
150 00 Prague 5, Czech Republic
Office:
Tel: + 420 224 942 575
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www.cbttravel.cz/ceesummit
e-mail: peckova@cbttravel.cz

CBT
CONGRESS BUSINESS TRAVEL Ltd.

EMERGENCY NUMBER

Registration desk:
Zina Pecková + 420 606 918 277,
Lenka Parobková +420 775 369 404

SOCIAL PROGRAM

Friday, December 3, 2010
Dinner at the hotel restaurant
20.30 – 22.00

Saturday, December 4, 2010
Gala Dinner at the Kaiserštejnský Palác
20.00 – 23.30
Transfer is included

IVth Central European Osteoporosis Summit Program

Start time	End time	Session	Moderator	Topics	Presenter	Time minutes
December 3, 2010						
20.00	20:30	**Plenary lecture**	**Hans Didier**	**Highlights from the Position Development Conference**	Catalina Poiana	**30**
20:00	22:00	**Welcome dinner (at the hotel)**				
December 4, 2010						
8:30	8:40	General	Vladimir Palicka	**Introduction**	Vladimir Palicka/Heinrich Resch	10
8:40	8:55			Review of the 2nd and 3rd Osteoporosis Summit outcomes	Heinrich Resch/Peter Lakatos	15
8:55	9:25	Vitamin D	Csaba Horvath	Invited lecture: Vitamin D supplementation - skeletal and extra skeletal effects	Meinrad Peterlik	30
9:25	9:40			Vitamin D estimation - what we measure and how	Vladimir Palicka	15
9:40	9:55	**Coffee break**				15
9:55	10:15	Vitamin D	Csaba Horvath	Target Level of Vitamin D supplementation	Heinrich Resch	20
10:15	10:35			Effects of Vitamin D supplementation - Benefits	Edward Czerwinski	20
10:35	10:55			Vitamin D supplementation - secondary osteoporosis	Sylvie Dusilova Sulkova	20
10:55	11:15			Discussion		20
11:15	11:45	Invited lecture		Invited lecture: Preclinical observation with osteoporosis drugs	Serge Ferrari	30
11.45	12.45	**Lunch Break/ Posters**				60
12.45	13.00	Poster	Roman Lorenc	Posters presentations	Selected	15
13.00	13.25	Risk/Benefit of Osteoporosis treatment	Heinrich Resch	Denosumab treatment benefit	Peter Gillberg	25
13.25	13.50			Denosumab treatment risks	Waldemar Misiorowski	25
13.50	14.10			Discussion		20
14.10	14:35		Serge Ferrari	Calcium supplementation - benefits	Tzvetanka Petranova	20
14:35	14.55			Calcium supplementation - risks	Meinrad Peterlik	20
14.55	15.15			Discussion		20
15.15	15.35			Bisphosponates therapy - benefits	Gerald Holzer	20
15.35	15.55			Bisphosponates therapy - risks	Alexander Dreval	20
15.55	16.15			Discussion		20
16.15	16.30	**Coffee break**				15
16.30	16.50	Osteoporosis guidlines	Vladimir Palicka/ Heinrich Resch	Swiss Osteoporosis guidelines - practice sharing	Rene Rizzoli	20
16.50	17.10			HU, AU, SK and CZ Osteoporosis guidelines examples	P. Lakatos; H. Resch; J. Payer; V. Palicka	20
17.10	17.45			Discussion (country practice sharing)		35
17.45	18.00	General		Closing remarks	Vladimir Palicka/Heinrich Resch	15
20.00	22.00	**Dinner (downtown)**				

SCIENTIFIC BOARD:

Resch Heinrich – Austria
Palicka Vladimir – Czech
Lorenc Roman– Poland
Lakatos Peter – Hungary

LIST OF SPEAKERS

Plenary lecture:

Poiana Catalina

Invited lectures:

Ferrari Serge
Peterlik Meinrad
Rizzoli Rene

Speakers:

Czerwinski Edward
Dreval Alexander
Dusilova Sulkova Sylvie
Gillberg Peter
Holzer Gerald
Lakatos Peter
Misiorowski Waldemar
Palicka Vladimir
Payer Juraj
Petranova Tzvetanka
Resch Heinrich

PLENARY LECTURE:

Poiana Catalina

Catalina Poiana, MD, PhD, FACE, CCD
Associate Professor of Endocrinology

Dr. Poiana is currently Associate Professor of Endocrinology at the "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania and Senior Endocrinologist in "C.I. Parhon" National Institute of Endocrinology from Bucharest. She received her medical degree (1984) and her PhD (1998) from "Carol Davila" University of Medicine and Pharmacy.

She is Fellow of the American College of Endocrinology since 2005, Full Faculty for the International Courses of Clinical Densitometry, organized by ISCD since 2006, NAMS Menopause Practitioner since 2008 and member of the NET-CME.net advisory board. Her research interest covers areas as: osteoporosis, menopause, ageing processes and endocrine tumors. She was acting as Principal Investigator in many RCT and as Project Assistant for "The European Research Area in Ageing" ERA-AGE, the EC Framework Six Program. She has more than 15 years of experience and expertise in the field of Medical Teaching and Research and is author and coauthor in more than 200 scientific papers.

Dr. Poiana is member in the Board of the Romanian Society of Endocrinology as well as a member in good standing in many international scientific societies, as AACE (*Member in the International Committee since 2010*), Endocrine Society, ISCD (*Member in the International Board between 2006-2009),* ECTS.

She received in 2009 *"John Bilezikian's ISCD Global Leadership Award"* for distinguished service and leadership in the global promotion of the field of bone densitometry and ISCD.

INVITED LECTURES:

Ferrari Serge

Prof. Dr. med. Serge Ferrari
Professor of Osteoporosis Genetics and Medicine, Geneva University Hospital, Geneva, Switzerland

Serge Ferrari is currently a Professor of Osteoporosis Genetics and Medicine at the Geneva Faculty of Medicine, and Medical Associate at the Department of Rehabilitation and Geriatrics of the Geneva University Hospital, Switzerland. He serves on the teaching committee of the Geneva Faculty of Medicine and teaches internal medicine, pathophysiology and bone metabolism to pre-graduate students.

Dr. Ferrari graduated from the Geneva University Faculty of Medicine in Switzerland in 1989, was Resident and Chief-Resident in Internal Medicine at the Geneva University Hospital, and then a post-doctoral fellow at Beth Israel Deaconess Medical Center in Boston (1997-2001), during which time he was appointed Instructor in Medicine at Harvard Medical School (2000).

He is president of the Swiss Bone and Mineral Society, founding member and on the board of directors of the International Society of Nutrigenetics and Nutrigenomics (ISNN), and member of the council of scientific advisors of the International Osteoporosis Foundation (IOF). Dr. Ferrari is a member of the editorial board of the *Journal of Bone and Mineral Research*, *Osteoporosis International* and *Bone*, and editor-in-chief of *BoneKEy*, an on-line journal and knowledge environment of the International Bone Mineral Society (IBMS). He is the recipient of many international awards, as well as three-time winner of the clinical research award from the Swiss Bone and Mineral Society.

Dr. Ferrari's current research interests include bone growth and fragility in childhood, genetics of osteoporosis, and the molecular mechanisms of PTH activity and bone remodelling. He has published more than 150 articles and book chapters in the bone field.

Peterlik Meinrad

Meinrad Peterlik, Ph.D., M.D.

Professor emeritus
Department of Pathophysiology
(formerly General and Experimental Pathology)
Medical University of Vienna, Austria
Date of birth: 5/23/38

Education:

University of Vienna, Austria	Ph.D.	1963	Chemistry
University of Vienna, Austria	M.D.	1972	Medicine
Cornell University (Ithaca, NY, USA)	-	1974/75	Postdoctoral training

Research and/or professional experience:

1983-2006	Full Professor of Pathophysiology, Head, Department of Pathophysiology
1978-83	Associate Professor of General and Experimental Pathology, University of Vienna Medical School, Austria
1974-75	Post-doctoral Fellow, Department of Physical Biology, NYS College of Veterinary Medicine, Cornell University, Ithaca, NY
1964-78	Research Associate, Department of General and Experimental Pathology, University of Vienna Medical School

Specialization

(i) Main field: Pathophysiology

(ii) Other fields: Biochemistry, Cell Biology

(iii) Current research interests: cellular actions of vitamin D; calcium and phosphate homeostasis; cytokines and bone turnover; hormonal regulation of intestinal cell differentiation; pathogenesis and treatment of colon cancer; pathogenesis of osteoporosis; hypovitaminosis D and calcium deficiency as causes for multiple chronic diseases

Rizzoli René

Prof. Dr. med. René Rizzoli

Professor of Medicine, Division of Bone Diseases, Department of Rehabilitation and Geriatrics, University Hospital, Geneva, Switzerland

René Rizzoli is an internist and endocrinologist, with a subspecialty focus on metabolic bone diseases, osteoporosis and disorders of mineral metabolism.

Dr. Rizzoli has been a chairman and president of several advisory and scientific committees and is presently a member of the Executive Committee of the International Osteoporosis Foundation. He is the chairman of the Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis.

Dr. Rizzoli is involved in both basic and clinical research projects investigating hormone action, regulation of bone growth, pathophysiology of osteoporosis and the role of nutrition, calcium, bisphosphonates, and other drugs in the prevention and treatment of osteoporosis. He has published more than 500 scientific articles and is an editor of *Bone* and an associate editor of *Osteoporosis International*.

SPEAKERS:

Czerwiński Edward

Professor Edward Czerwiński is the head of the Department of Bone and Joint Diseases at the Medical College of the Jagiellonian University as well as the Director of Krakow Medical Centre. He is an orthopaedic surgeon with 38 years of experience, including long term position as the head of the Department of Bone Surgery of the Jagiellonian University Hospital.

He has been involved in the research of bone and joint diseases for 27 years. His doctoral and postdoctoral theses were devoted to his first passion – fluorosis. The research was performed among workers of an aluminium steelworks who had been exposed to fluorine and a group of endemic fluorosis patients in India. For the last 17 years he has been engaged in the research of osteoporosis and osteoarthritis, which led to a number of projects in the field of epidemiology of osteoporosis, secondary osteoporosis and fractures in Poland. For many years Professor Czerwinski has been involved in international clinical trials of new medications for osteoporosis (alendronate, ibandronate, zoledronate, risedronate, denosumab, arzoxifen etc), degenerative joint disease (oral and intraarticular medications) and for many other diseases. He introduced new radiodensitometry methods and computer analysis of radiogram structure. Currently he is working on a fall prevention study and is performing an advanced research on the application of FRAX® in the Polish population. Together with Professor John Kanis he assessed an application of UK FRAX® model to Polish population and worked out the hand held FRAX® calculator.

For many years Professor Czerwinski worked abroad in such clinics as the Institute of Orthopaedics, Oswestry and The London Hospital Medical College. He organised 15 symposia and congresses in the field of orthopaedics and osteoporosis, including the first in Poland ICL European Federation of National Association of Orthopaedics and Traumatology. Since 1997 he has been organizing in Krakow the Central European Congress on Osteoporosis and Osteoarthritis. So far, 6,600 doctors from Poland and abroad participated in the Central European Congress on Osteoporosis and Osteoarthritis. The forthcoming congress is planned on 29 Sept – 1 Oct 2011.

Professor Czerwinski is the founder of the Krakow Branch of the Polish Osteoporosis Foundation and the Polish Osteoarthrology Society. He created the Polish Portal of Osteoporosis (www.osteoporoza.pl) and is an editorial board member of 9 scientific magazines as well as a member of 15 Polish and international scientific societies. Professor Czerwinski's output includes 360 publications.

Professor Czerwinski was nominated to the international expert board of EFORT/EULAR – guidelines for secondary fracture prevention and the ISCD-IOF FRAX Initiative – "Interpretation And Use Of FRAX® In Clinical Practice".

In his free time Professor Czerwinski enjoys lonely mountain walks, especially in Tatra and Bieszczady mountains, skiing in Poland and abroad, Polish lakes and exotic trips. His greatest passions are photography and music. (*more on: www.kcm.pl*)

Dreval Alexander

Dreval Alexander V., Professor, MD, PhD,
Head of Endocrinology Department at the Moscow Regional Scientific Research Clinical Institute named after Vladimirskiy (MONIKI), Chief endocrinologist at the Moscow region.

Alexander Dreval, born in 1947, graduated from Sechenov Moscow Medical Institute. After completing residency he entered post-graduate course and obtained PhD degree in 1974.

From 1974 till 1988 Prof. Dreval worked at the Sechenov Medical Academy starting with assistant position and then associate professor in the Endocrinology Department. In 1980 he graduated from the Applied Mathematics Department of the Moscow State University and was certified as qualified mathematician.

In 1990 he presented a dissertation and obtained the degree of a Doctor of Medical Sciences.

In 1996 he was awarded the rank of Professor of Endocrinology.

From1993 till present – Prof. Dreval is the head of the Endocrinology Department in MONIKI. Since 1995 he is the chief endocrinologist at the Moscow region.

Professor A. Dreval is the author of 201 research papers (189 in the co-author), 4 books, 4 of textbooks, as well as the author of two diabetes websites.

Among research interests of Prof. Dreval are the following: optimizing treatment and diagnosis of diabetes and its complications, treatment and prevention of osteoporosis, the epidemiology of endemic goiter and prophylaxis, radioiodine therapy of diffuse toxic goiter in the young patients, endocrine ophthalmopathy, mathematical modeling of endocrine systems, information technology in medicine – diabetes mellitus in particular, online projects for the patients and medical professionals.

As qualified mathematician Prof. Dreval developed a number of original models of diabetes, revealing the key role of the liver in the development of particular forms. With the help of a mathematical approach he proposed a unique method of analyzing the results of intravenous glucose tolerance test to determine hepatic glucose production in normal state and diabetes.

Prof. Dreval actively implements in practice Informational technologies (Internet sites), creating specialized diabetes sites for physicians, researchers and people suffering from diabetes.

Prof. Dreval combines clinical and research activity with the administrative position of the chief endocrinologist of Moscow Region. His activity is concentrated on the three socially significant areas: diabetes, thyroid disease and osteoporosis.

Prof. Dreval is the member of the National Advisory Board on “Diabetes program” and of the editorial boards of scientific research journals: “Problems of Endocrinology,” Osteoporosis” and “ Andrology”.

Dusilova Sulkova Sylvie

Sylvie Dusilova Sulkova, M.D., DSc., prof.
Graduated at First Medical Faculty, Charles University, Prague (1980). Qualified in internal medicine (1984 and 1988) and in nephrology (1992). Ph.D. thesis on the topic of renal bone disease (1991); DSc. thesis on the topic of continuous monitoring during hemodialysis (2001). Professor of internal medicine at Charles University (2003). In 1997-2004, head of Department of Internal Medicine Strahov, 1st Medical Faculty and General Faculty Hospital, Prague (head of Dialysis Unit Strahov 1989-2004). In 2006-2010, head of Academic Dept of Nephrology, Medical Faculty in Hradec Králové. Since April 2010, head of Clinical Unit, Department of Nephrology, Institute for Clinical and Experimental Medicine, Prague. President of Czech Society of Nephrology (2004-2006), scientific secretary of Czech Society of Nephrology (1998-2004; since 2010). Since 2006 Editor in chief of the journal News in nephrology (Aktuality v nefrologii; in Czech). Main scientific interests - disorder of calcium and phosphate metabolism in chronic kidney disease, including dialysis and kidney transplant patients; renal replacement therapies. Author or co-author of approx. 100 scientific articles (SCI above 300). Main author of several monographies, including Hemodialysis (2000), Peritoneal Dialysis (1993; 2007 – Award of Czech Society of Nephrology) and Renal osteodystrophy (2007).

Gillberg Peter

Dr Peter Gillberg MD PhD.

Peter graduated from Stockholm University Karolinska Institute, Sweden 1988. He is a board certified specialist in endocrinology and internal medicine. He spent six years as a faculty member in the Division of Endocrinology at the University Hospital in Uppsala Sweden. His primary responsibilities included teaching at the Medical Faculty and development of the Osteoporosis Outpatient unit. In addition he is sub-specialized in osteoporosis and has served as head for the Osteoporosis unit at the University Hospital in Örebro, Sweden. In addition he has a number of publications and holds a PhD in the field of male osteoporosis. Peter is also still active as an osteoporosis specialist and provides ongoing input to male osteoporosis guidelines in Sweden. Peter joined Amgen from Sanofi-Aventis, Sweden where he was a Medical Manager with the overall responsibility for bone, diabetes and cardiovascular diseases. Prior to that, he was working in Astra Zeneca's Headquarter in Sweden as a Global Drug Safety Physician with responsibility for products in the diabetes and pain area. Peter joined Amgen in 2009 as the Therapeutic Area Head, Bone, in the Nordic Baltic region. Since June 2010 he is International Medical Lead for Prolia.

Holzer Gerold

Prof. Dr. Gerold Holzer

Medical University of Vienna

Curriculum vitae

1957 born on Dec. 17th

1976 Graduation Gymnasium

1975 – 1977 Five times Austrian Champion in Swimming

1986 Medical Doctor University of Vienna

1987 Training in Orthopaedic Surgery

1992 „Scientific Award of the Medical-Scientific Society for Carinthia and East Tyrol"

1992 – 1996 Training in Orthopaedic Surgery, Department of Orthopaedic Surgery University of Vienna (Head: Prof. Dr. R. Kotz)

1995 Board Certification „Orthopaedic Surgeon" Head „Osteoporosis Outpatient s Department, Department of Orthopaedic Surgery, University of Vienna Guest Professor Department of Orthopaedic Surgery, Yamagata University, Japan

1997 – 1998 Fellowship "Max Kade Foundation", New York Research Professor at The Mount Sinai School of Medicine, New York, Department of Orthopaedic Surgery, Orthopaedic Research Laboratory, Prof. Dr. TA. Einhorn, Prof. Dr. RJ. Majeska

1997 "Board of National Societies" of the "European Foundation for Osteoporosis"

1998 until today Department of Orthopaedic Surgery, Medical University of Vienna (Head: Prof. Dr. R. Kotz, Prof. R. Windhager) Head Orthopaedic Outpatient s Department Neuromuskular Diseases Department of Neuropsychiatry of Children and Adolescence, Medical University of Vienna

2002 Habilitation in Orthopaedics (similar to Ph. D.) University of Vienna; Member „International Osteoporosis Foundation" European Union Consultation Panel

2003 Associate Professor, Department of Orthopaedic Surgery, Medical University of Vienna

1999 – 2006 Guest Professor „Issues of Osteoporosis in Orthopaedics", Department of Orthopaedics, Boston University School of Medicine

2005 – 2006 Consultant Federal Ministry for Health and Women, Austrian EU Presidency, Preparation Council Conclusion „Osteoporosis“

2009 “Researcher of the Month September” Medical University of Vienna

2010 Organizer Training Course “Osteoporosis” Austrian Society of Orthopaedics and Orthopaedic Surgery

Lakatos Peter

Prof. Peter Lakatos

Professor of Medicine and Endocrinology, Semmelweis University, Budapest, Hungary

After studies in biology and chemistry, Dr. Peter Lakatos finished medical school at the Semmelweis University, Budapest, in 1981. He started his medical career at the 1st Department of Medicine, Semmelweis University. Between 1989 and 1992 he worked with Prof. Paula Stern at the Department of Pharmacology, Northwestern University, Chicago, studying intracellular signal transduction in bone cells. After that, he returned to the Semmelweis University but remained a faculty member at the Northwestern University until 1998. Currently, he is a full professor of medicine and endocrinology, as well as head of the Clinical Research Laboratory, at the Semmelweis University.

Dr. Lakatos and his research group have actively participated in the development and introduction of biochemical and densitometric methods in the management and research of osteoporosis. In the 80’s, he was among first to develop an osteocalcin radioimmunoassay. He directs basic and clinical research programs in the field of metabolic bone diseases with a special interest in osteoporosis and thyroid hormone-stimulated bone loss. During the last decade, his major interest has been in the genetic background of metabolic bone diseases. Dr. Lakatos also conducts drug development studies. He has authored more than 270 full length scientific articles and book chapters. Amongst other posts, Dr. Lakatos has acted as the President of the Hungarian Society for Osteoporosis and Osteoarthrology (1999-2005) and was a board member of the European Society for Calcified Tissues (1997-2007).

Misiorowski Waldemar

Waldemar Misiorowski M.D., Ph.D. is currently Senior Lecturer and Senior Consultant of the Department of Endocrinology, Medical Center for Postgraduate Education, Warsaw, Poland. He completed his studies at the Warsaw Medical University, where he obtained the degree of the Doctor of Medicine in 1979. He received his PhD in Medical Sciences in 1988 at the Medical Center for Postgraduate Education, and was board certified for Internal Medicine in 1989 and for Endocrinology in 1995.

His main field of interest include the diagnosis and treatment of osteoporosis, and calcium & bone metabolic disorders with a special focus on primary hyperparathyroidism, hypercalcemia of malignancy, and hypovitaminosis D. He is the author and co-author of many scientific and educational articles. Dr Misiorowski actively participate in the development of guidelines for the management of osteoporosis, primary hyperparathyroidism, and hyperparathyroidism in Poland.

Dr Misiorowski is a Board Member of the Polish Menopause and Andropause Society, and Polish Society of Anti-Aging Medicine. He is also an active member of Polish Endocrine Society and Multidisciplinary Osteoporosis Forum. Lecturer at IOF and ISCD regional Training Courses on Osteoporosis and Densitometry.

Palička Vladimír

Professional CV – Vladimír Palička

Born 1946 in Prostejov. He graduated from the Medical Faculty of Palacky University in Olomouc, Department of General Medicine and graduation in 1970. Then many years of experience in hospital practice Bruntál with the internal, surgical ward and subsequently the Department of Clinical Biochemistry. Since 1984 he has been University Hospital and Medical Faculty of Charles University in Hradec Kralove.
Education:

- degree in Clinical Biochemistry, Postgraduate Diploma in Endocrinology 2001
- candidate of medical sciences 1985 (secondary metabolic effects of hormonal contraception)
- Associate Professor of Biochemistry (1990)
- Associate Professor of Internal Medicine 2000 (habilitation)
- Professor of Internal Medicine 2001

Clinical and scientific positions:

- Dean of the Medical Faculty of Charles University in Hradec Kralove 2004-2010
- Head of the Department of Clinical Biochemistry and Diagnostics, Faculty Hospital Hradec Kralove
- Head of the Osteocentrum Hradec Kralove

Membership and positions in scientific societies:

- Vice-President of the Czech Medical Association JE Purkyne
- Honorary President of the Czech Society of Clinical Biochemistry CLS JEP
- President of the Society for Metabolic Bone Diseases CLS JEP
- Former Vice-President of the World Committee of Clinical Chemistry and Laboratory Medicine (IFCC)
- Past-President of the Forum of European Societies of Clinical Chemistry
- European Society for parenteral and enteral Nutrition – Member
- American Association for Clinical Chemistry – Member
- Association of Clinical Biochemists of the UK – Member
- Slovak Society of Clinical Biochemistry – honorary member
- Czech Society for Rheumatology – honorary member
- Honorary Member Hungarian Society for Clinical Pathology – Honorary Member of
- Polish Society for Laboratory Diagnostics – Honorary Member Polish Society of Laboratory Diagnostics – Honorary Member of
- Scientific Council of the Ministry of Health – Chairman
- Scientific Council of Faculty of Medicine in Hradec Kralove – Member
- Scientific Council of Palacky University in Olomouc – Member
- Scientific Council of the Pharmaceutical Faculty of Charles University in Hradec Kralove – Member
- Scientific Board of the Czech Medical Chamber – member

Member of the Editorial Board (or its range) journals:

- Nutrition International (USA
- Annals of Clinical Biochemistry (UK)
- Clinical Chemistry and Laboratory Medicine (D) Clinical Chemistry and Laboratory Medicine (D)
- Advances in Clinical Pathology (I)
- Biochemia Medica (Croatia) Biochemistry Medica (Croatia)
- Revista Romana de Medicina de Laborator (R)
- Klinická biochemie a metabolismus (ČR) Clinical biochemistry and metabolism (CR)
- Osteologický Bulletin (ČR) Osteological Bulletin (CR)
- Postgraduální medicína (ČR) Postgraduate Medicine (CR)
- Remedia (ČR) Remedia (CR)
- Biomarkers and Environment (ČR) Biomarkers and Environment (CR)
- Klinická mikrobiologie a infekční lékařství (ČR) Clinical Microbiology and Infectious Diseases (CR)
- Ošetřovatelství (ČR) Nursing (CR)
- a několika dalších. and several others.

Publications and research activity:

- He has published more than 400 works of Czech and foreign professional literature, including chapters in books. He is author or coauthor of more than 600 lectures and poster presentations, more than 150 countries.
- Investigator and Associate Investigator of several tens of research projects and grants.

Payer Juraj

Prof. Juraj PAYER, M.D., PhD.

Curriculum Vitae

Personal details

Date of birth: 13. 03. 1958 Bratislava
Nationality: slovak
Address: Drieňova 1/H, Eden Park, Bratislava
Email: payer@ruzinov.fnspba.sk
Telephone: +421 2 905 455 079
Fax: +421 2 48 234 110

Education & Qualifications

2002	Medical Faculty, Comenius University in Bratislava *professor of internal medicine*
1997	Medical Faculty, Comenius University in Bratislava *associated professor of internal medicine*
1997	Institutional postgraduate specialization qualifications and life-long education in medical disciplines, Bratislava

	Accreditation in Internal medicine grade II
1994	Medical Faculty, Comenius University in Bratislava PhD study
1990	Institutional postgraduate specialization qualifications and life-long education in medical disciplines, Bratislava
	Accreditation in Endocrinology
1986	Institutional postgraduate specialization qualifications and life-long education in medical disciplines, Bratislava
	Accreditation in Internal medicine grade I.
1977 – 1983	Medical Faculty, Comenius University in Bratislava *General Medicine*
1974 – 1977	Secondary Grammar School – Gymnazium L. Sáru Bratislava

Work Experience

2006 – present	5th Department of Internal Medicine, Medical Faculty of Comenius University and Faculty Hospital in Bratislava
	Head of the department
2004 – 2006	Department of Internal Medicine, Hospital in Bratislava
	Head of the department
1983 – 2004	1st Department of Internal Medicine, Medical Faculty of Comenius University and Faculty Hospital in Bratislava
	Head of the Endocrinological Department, Teacher

Professional memberships:

- Main expert in endocrinology, Ministry of Health Care of the Slovak Republic
- Vice-president of Slovak Endocrine Society
- President Osteoporosis and Metabolic Bone Diseases Society (SOMOK)
- Member of presidium of Slovak Medical Society

Publications:

more than 12 books

more than 306 publications

more than 244 citations

Petranova Tzvetanka

Tzvetanka Petranova, MD

Chief assistant at the Clinic of Rheumatology
Medical University, Sofia
Bulgaria

Tzvetanka Petranova received her medical degree from the University of Pleven, Bulgaria in 1986. She became a specialist in Internal Diseases in 1993, in Rheumatology in 1995. Since 1995 she works as a chief assistant at the Clinic of Rheumatology at the Medical University in Sofia, where beside clinical duties, she teaches Internal Diseases and Rheumatology to students and postgraduate physicians.

Her research work in the past 15 years has focused on osteoporosis, with special focus on glucocorticoid-induced osteoporosis. She has 21 publications in the area. She is responsible for the organization of the annual postgraduate osteoporosis course.

Another field of interest in the past 5 years is the musculoskeletal ultrasound/MSUS/. She has 17 publications in the area. Again, she is in charge of the national course on MSUS.

Dr. Petranova is a fellow of Bulgarian Society of Rheumatology, Bulgarian Society of ODM /Osteodensitometry/, Bulgarian Society of Osteoporosis and Osteoarthritis, Bulgarian union of medical doctors.

Resch Heinrich

Heinrich Resch, M.D. Professor of Medicine

University Vienna, School of Medicine
Head, Medical Department II (Osteology/Rheumatology& Gastroenterology)
Krankenhaus der Barmherzigen Schwestern (St. Vincent Hospital)
Academic Teaching Hospital of the University Vienna
Stumpergasse 13, 1060 Vienna, Austria

Past President of the German Society of Osteology (DGO)
President Elect of the Austrian Society of Bome and Mineral Research (AuSBMR)

Personal Statistics:
Date of birth: March 2, 1957
Place of birth: Vienna, Austria
Marital status: married, 2 children

Education
School-leaving exam, Stiftsgymnasium Seitenstetten College, 1975
M.D. Vienna University, School of Medicine, 1981

Present Position
Professor of Medicine, School of Medicine, University Vienna,
Chief, Medical Department II (Rheumatology & Gastroenterology)
Krankenhaus Barmherzige Schwestern (St. Vincent Hospital)
Academic Teaching Hospital, Medical University Vienna
Stumpergasse 13, 1060 Vienna, Austria
Head, VINforce Study Group
Head IRNO (Imaging Research Network in Osteology) Vienna

Previous Positions
Intern, General Hospital Vienna Department of Gastroenterology, Nephrology, Rheumatology 1983/84
Resident hospital doctor, KH Barmherzige Brüder (St. John of God) 1984 – 1991
Postdoctoral Research Fellow, Loma Linda University, CA, USA 1992/93
Research Fellow, Vienna University, Department of Experimental and Clinical Pathology 1994
Chief, Department of Physiotherapy & Rehabilitation, Krankenhaus Barmherzige Schwestern (St. Vincent Hospital)

Scientific work
basic and clinical research in bone metabolism, approximately 100 publications in national and international journals and book chapters, more than 150 invited lectures, review panel Bone, Eur J Radiology, Int J Mens Health Gender, Maturitas

Professional Organisations

1987 Ludwig Boltzmann-Institution of Advancing Age

1988 Austrian Society of Gastroenterology and Hepatology

1991 Founding Member and Member of the Board of the Austrian Society of Bone and Mineral Research

1992 American Society for Bone and Mineral Research

1993 German Society of Endocrinology

1994 German Society of Osteology

1994 Editor in Chief Journal für Mineralstoffwechsel (J Mineral Metabolism)

1995 Member of the Austrian Society of Rheumatology

1998 International Society of Bone research

2001 Founding Member of the Austrian Bone & Joint Decade

2002 Editorial Board and Co-editor of the journal *Osteologie*

2003 Board Member of the Austrian Society of Rheumatology

2003 Vice-President of the DGO (Deutsche Gesellschaft für Osteologie – German Society of Osteology

2004 International Scientific Advisor of the University Teheran(Iran)

2005 President of the German Society of Osteology

2006 Chairman of the EU Summit Conference on Diagnosis and Treatment of Osteoporosis

2007 Chief Editor of the Journal of Osteology
Member of the CNS (IOF) and the Osteoporosis Panel of the EU Parliament
Series guest editor Int Journal of Mens Health &Gender

2008 President Elect of the Austrian Society of bone and Mineral Research (AuSBMR)

2009 Appreciation Award of the Bahrainan Society for Osteoporosis

2010 Member of the Greek Society of Bone and Mineral Research
Honorary Member of the Ukrainian Osteoporosis Society

2010 Honorary Member of the Slovakian Medical Society

SUMMIT PROGRAM

December 3, 2010

20.00 – 20.30	**Plenary lecture (at the hotel restaurant)**
	Moderator: Hans Didier
	Catalina Poiana: Highlights from the Position Development Conference
20.30 – 22.00	**Welcome dinner (at the hotel)**

December 4, 2010

	General session
	Moderator: Vladimir Palicka
08.30 – 08.40	Vladimír Palicka / Heinrich Resch: Introduction
08.40 – 08.55	Heinrich Resch / Peter Lakatos: Review of the 2nd and 3rd Osteoporosis Summit outcomes
	Session Vitamin D
	Moderator: Csaba Horvath
08.55 – 09.25	**Invited lecture**
	Meinrad Peterlik: Vitamin D supplementation – skeletal and extra skeletal effects
09.25 – 09.40	Vladimir Palicka: Vitamin D estimation – what we measure and how
09.40 – 09.55	**Coffee break**
	Session Vitamin D
	Moderator: Csaba Horvath
09.55 – 10.15	Heinrich Resch: Target Level of Vitamin D supplementation
10.15 – 10.35	Edward Czerwinski: Effects of Vitamin D supplementation – Benefits
10.35 – 10.55	Sylvie Dusilova Sulkova: Vitamin D supplementation – secondary osteoporosis
10.55 – 11.15	Discussion
11.15 – 11.45	**Invited lecture**
	Serge Ferrari: Preclinical observation with osteoporosis drugs
11.45 – 12.45	**Lunch break / Posters**
12.45 – 13.00	**Poster presentations**
	Moderator: Roman Lorenc
	Session Risk / Benefit of Osteoporosis treatment
	Moderator: Heinrich Resch
13.00 – 13.25	Peter Gillberg: Denosumab treatment benefit

13.25 – 13.50	Waldemar Misiorowski: Denosumab treatment risks
13.50 – 14.10	Discussion
	Session Risk / Benefit of Osteoporosis treatment
	Moderator: Serge Ferrari
14.10 – 14.35	Tzvetanka Petranova: Calcium supplementation – benefits
14.35 – 14.55	Meinrad Peterlik: Calcium supplementation – risks
14.55 – 15.15	Discussion
15.15 – 15.35	Gerald Holzer: Bisphosponates therapy – benefits
15.35 – 15.55	Alexander Dreval: Bisphosponates therapy – risks
15.55 – 16.15	Discussion (20 min.)
16.15 – 16. 30	**Coffee break**
	Session Osteoporosis guidlines
	Moderator: Vladimir Palicka / Heinrich Resch
16.30 – 16.50	Rene Rizzoli: Swiss Osteoporosis guidelines – practice sparing
16.50 – 17.10	P. Lakatos; H. Resch; J. Payer; V. Palička:
	HU, AU, SK and CZ Osteoporosis guidelines examples
17.10 – 17.45	Discussion / country practice sharing
17.45 – 18.00	**General session**
	Vladimír Palicka, Heinrich Resch: Closing remarks
19.30	Transfer to Kaiserštejnský Palác
20.00 – 23.30	Gala-dinner at the Kaiserštejnský Palác
	Return transfer by bus

December 5, 2010

Transferes for the airport

IMPORTANT NOTE

Final electronic version of the Congress Book will be available on SMOS website **http://www.smos.cz**

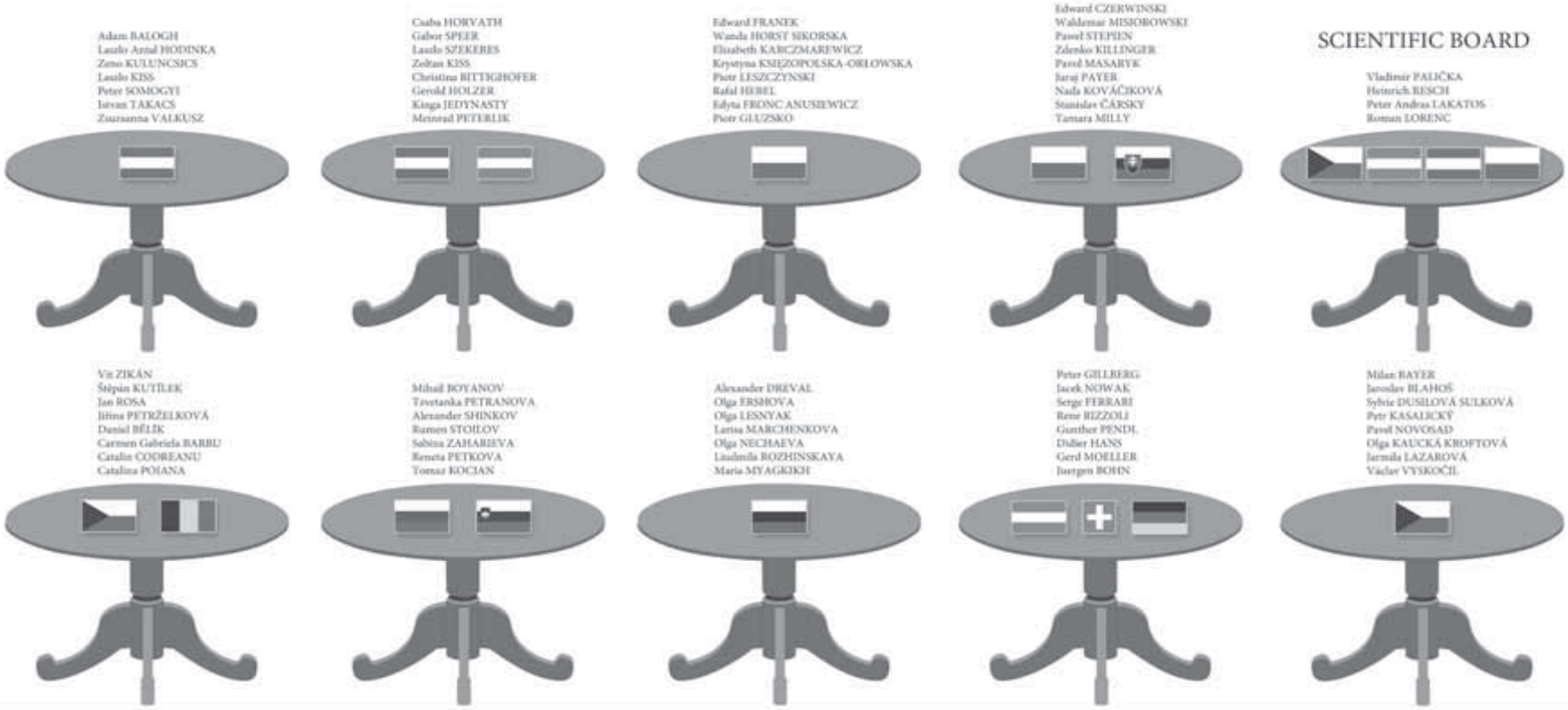
LIST OF PARTICIPANTS

Bittighofer	Christina	Austria
Holzer	Gerold	Austria
Jedynasty	Kinga	Austria
Nowak	Jacek	Austria
Peterlik	Meinrad	Austria
Resch	Heinrich	Austria
Boyanov	Mihail	Bulgaria
Petkova	Reneta	Bulgaria
Petranova	Tzvetanka	Bulgaria
Shinkov	Alexander	Bulgaria
Stoilov	Rumen	Bulgaria
Zaharieva	Sabina	Bulgaria
Bayer	Milan	Czech Republic
Bělík	Daniel	Czech Republic
Blahoš	Jaroslav	Czech Republic
Dusilová Sulková	Sylvie	Czech Republic
Kasalický	Petr	Czech Republic
Kaucká Kroftová	Olga	Czech Republic
Kutílek	Štěpán	Czech Republic
Lazarová	Jarmila	Czech Republic
Novosad	Pavel	Czech Republic
Palička	Vladimír	Czech Republic
Petrželková	Jiřina	Czech Republic
Rosa	Jan	Czech Republic
Vyskočil	Václav	Czech Republic
Zikán	Vít	Czech Republic
Bohn	Juergen	Germany
Balogh	Adam	Hungary
Hodinka	László Antal	Hungary
Horvath	Csaba	Hungary
Kiss	Laszlo	Hungary
Kiss	Zoltan	Hungary
Kuluncsics	Zeno	Hungary
Lakatos	Peter Andras	Hungary
Somogyi	Péter	Hungary
Speer	Gabor	Hungary
Szekeres	László	Hungary
Takacs	Istvan	Hungary
Valkusz	Zsuzsanna	Hungary
Czerwinski	Edward	Poland
Franek	Edward	Poland
Fronc	Anusiewicz Edyta	Poland
Gluszko	Piotr	Poland

Hebel	Rafal	Poland
Horst-Sikorska	Wanda	Poland
Karczmarewicz	Elizabeth	Poland
Księzopolska-Orłowska	Krystyna	Poland
Leszczynski	Piotr	Poland
Lorenc	Roman	Poland
Misiorowski	Waldemar	Poland
Stepien	Pawel	Poland
Barbu	Carmen Gabriela	Romania
Codreanu	Catalin	Romania
Poiana	Catalina	Romania
Dreval	Alexander	Russia
Ershova	Olga	Russia
Lesnyak	Olga	Russia
Marchenkova	Larisa	Russia
Myagkikh	Maria	Russia
Nechaeva	Olga	Russia
Rozhinskaya	Liudmila	Russia
Čársky	Stanislav	Slovakia
Killinger	Zdenko	Slovakia
Kováčiková	Naďa	Slovakia
Masaryk	Pavol	Slovakia
Milly	Tamara	Slovakia
Payer	Juraj	Slovakia
Kocjan	Tomaz	Slovenia
Ferrari	Serge	Switzerland
Gillberg	Peter	Switzerland
Hans	Didier	Switzerland
Moeller	Gerd	Switzerland
Pendl	Gunther	Switzerland
Rizzoli	Rene	Switzerland

MEETING ROOM – SEATING PLAN

4TH EUROPEAN OSTEOPOROSIS SUMMIT
CENTRAL EASTERN EUROPE



THE MEETING IS ORGANIZED BY SMOS AND AUSTRIAN SOCIETY OF OSTEOPOROSIS

AUSTRIAN SOCIETY OF OSTEOPOROSIS

SUMMIT SECRETARIAT

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POSITION PAPER

Management of osteoporosis in central and eastern Europe (CEE): conclusions of the "2nd Summit on Osteoporosis—CEE", 21–22 November 2008, Warsaw, Poland

Roman S. Lorenc · Heinrich Resch · on behalf of the Members of the "2nd Summit on Osteoporosis—Central and Eastern Europe (CEE)"

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Abstract In November 2008, the "2nd Summit on Osteoporosis—Central and Eastern Europe (CEE)" was held in Warsaw, Poland. Discussions at this meeting focused on the identification and discussion of diagnostic, preventive, and therapeutic measures used in CEE. Evaluated information was used to identify issues regarding diagnosis and therapy of osteoporosis in these countries to facilitate the subsequent setup of appropriate support and development strategies. The main debate was structured according to the following five subjects: (1) present status and future perspectives for implementation of FRAX® into local (CEE) diagnostic algorithms, (2) principles of drug selection in osteoporosis treatment in CEE countries, (3) nonpharmacological interventions in osteoporosis treatment and prophylaxis in CEE countries, (4) treatment benefit evaluation, and (5) cost–effectiveness and evaluation of reimbursement policies in CEE countries. The most important and substantial comments of the delegates are summarized in the present article. The multinational panel of experts with representatives from many CEE countries as well as Austria and Switzerland made the "2nd Summit on Osteoporosis—CEE" a perfect platform to identify issues and needs regarding diagnosis and therapy of osteoporosis as well as the cost–effectiveness of osteoporosis management in CEE countries. The information gained will serve as a basis for the development of strategies to resolve the identified issues at the "3rd Summit on Osteoporosis—CEE" in November 2009.

Keywords Central and eastern Europe · FRAX® · Diagnosis of osteoporosis · Treatment of osteoporosis · Health economics · Treatment benefit

R. S. Lorenc (✉)
Department of Biochemistry & Experimental Medicine,
The Children's Memorial Health Institute,
Al. Dzieci Polskich 20,
04-730 Warsaw, Poland
e-mail: biochemia@czd.pl

H. Resch
Medical Department (Rheumatology/Osteology & Gastroenterology), St. Vincent Hospital Vienna,
Medical University of Vienna,
Vienna, Austria

Introduction

In Europe, USA, and Japan, about 75 million people suffer from osteoporosis [1]. During their lifetime, up to 50% of women and 30% of men will experience an osteoporosis-related fracture [2]. Particularly in the case of hip fractures, immediate hospitalization is required that is quite often followed by a long and problematic recovery; in addition, a substantial number of patients become permanently disabled after such a fracture. This protracted course of the disease means that not only the patients' quality of life is considerably impaired but also that the costs for acute therapies and postoperative measures including rehabilitation are substantial. Hence, osteoporosis is one of the most serious chronic diseases that causes an enormous financial burden.

Because of their often serious consequences, prevention of fractures is the main goal of osteoporosis therapy. Prerequisite to achieve this goal is the identification of patients at risk for fractures by adequate diagnostic measures. Osteoporosis is characterized by low bone mineral density (BMD) [3]. Based on this parameter, guidelines for therapeutic interventions recommend assess-

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ing BMD for the diagnosis of osteoporosis [4, 5]. The risk of fracture, however, is caused multifactorially, including risk factors such as age, prior fragility fractures, a parental history of hip fracture, smoking, use of systemic corticosteroids, excess alcohol intake, and rheumatoid arthritis [6, 7]. Therefore, BMD together with these factors should be considered when the fracture risk of an individual patient is evaluated [6, 7]. Recently, the computer-based tool for fracture risk calculation (FRAX®, http://www.shef.ac.uk/FRAX/) has been developed. The algorithm of this tool takes this multifactorial approach into account. While rather simple to use, FRAX® generates very reliable data on the individual fracture risk. Based on such information, physicians can then decide on the appropriate measures to be taken to prevent fractures.

In clinical practice, however, the diagnostic and therapeutic challenges of osteoporosis therapy are not always met. In fact, a substantial proportion of individuals at high risk, who have already had at least one fragility fracture, including hip fractures [8, 9], are neither appropriately diagnosed nor treated for probable osteoporosis [10–12]. Simplifying the diagnostic procedure by such easy-to-use tools as FRAX® might increase the diagnosis rate of osteoporotic patients and support the timely administration of the required treatments. This tool, however, is not yet available in every country.

Therefore, the discussions at the "2nd Summit on Osteoporosis—Central and Eastern Europe (CEE)" concentrated on the need for appropriate discrimination and evaluation of the individual osteoporosis risk factors to maximize the benefits of pharmacotherapy while limiting the risks and costs that accompany treatment. Here, the major aim was to identify and discuss diagnostic, preventive, and therapeutic measures used in CEE. A comprehensive analysis covering these aspects in all CEE countries is not yet available, most probably because of considerable differences between the individual countries not only regarding culture, living conditions, life expectancy but also regarding availability and use of medical treatment for osteoporosis and, finally, reimbursement.

Representatives from Austria and Switzerland but mainly from CEE countries including the Czech Republic, Hungary, Poland, Romania, Slovakia, and Slovenia participated in the "2nd summit on Osteoporosis—CEE". This multinational panel of experts made the meeting a perfect platform to develop the above topics. Discussion was based on six international reference publications [13–18]; the main debate was structured according to the following five subjects:

1. Present status and future perspectives for implementation of FRAX® into local (CEE) diagnostic algorithms
2. Principles of drug selection in osteoporosis treatment in CEE countries
3. Nonpharmacological interventions in osteoporosis treatment and prophylaxis in CEE countries
4. Treatment benefit evaluation
5. Cost–effectiveness and evaluation of reimbursement policies in CEE countries

The information evaluated during the summit was used to identify issues regarding diagnosis and therapy of osteoporosis in CEE countries to facilitate the subsequent setup of appropriate support and development strategies. The most important and substantial comments of the delegates are summarized below.

Present status and future perspectives for implementation of FRAX® into local (CEE) diagnostic algorithms

The computer-based tool FRAX® has been developed by the WHO from studying population-based cohorts from Europe, North America, Asia, and Australia to evaluate the fracture risk of patients (http://www.shef.ac.uk/FRAX/). It is based on individual patient models that integrate the risks associated with clinical risk factors as well as BMD at the femoral neck. FRAX® represents a very sensitive tool to identify patients with a high fracture risk; its output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). Use of FRAX® for fracture risk calculation is recommended by current European guidelines [15] as well as by guidelines of the National Osteoporosis Foundation and the World Health Organization (WHO) [19] to improve diagnosis, facilitate the decision for appropriate therapeutic interventions, and, in the long run, save costs by fracture prevention.

Prerequisite for the implementation of FRAX® in a specific country is information on the local epidemiology of fractures and death. In several countries including UK, Germany, Sweden, Japan, the USA, and others, sufficient reliable epidemiological data are available to calculate the fracture risk of an individual patient by FRAX®. In countries where such epidemiological data are missing, the guidelines for the use of FRAX® recommend to "use (the FRAX® model of) the country for which the epidemiology of osteoporosis most closely approximates your country." (http://www.shef.ac.uk/FRAX/). However, this approach is in a way problematic because the incidence of hip fractures and death differ considerably (10- to 15-fold) between countries [20–22]. Hence, to obtain reliable information on fracture risk by FRAX®, local data on fracture and death rates should be assessed before implementation of FRAX® in a specific country.

Comments of the delegates on the use of FRAX® in CEE countries

Expectations from FRAX® in CEE countries The final aim of any interventional procedure in osteoporosis is the development of a uniform, diagnostic, therapeutic, and cost–effective algorithm of treatment and fracture prevention.

FRAX® has been developed as a 10-year fracture risk calculator based on femoral neck densitometry (or BMD) and available independent clinical fracture risk factors. FRAX® generally does not change WHO diagnostic classification of osteoporosis; however, with its use, we can expect that a lower number of younger patients at low risk as well as a higher number of elderly patients at high risk will be selected for treatment.

FRAX® can be a helpful screening tool in general practitioner case-finding strategies to identify patients with a high fracture risk (diagnostic threshold) without the use of densitometry or with only limited access to densitometry.

Specific issues regarding the use of FRAX® in CEE countries The audience agreed that presently, there are insufficient, satisfactorily validated studies concerning spine densitometry and fracture rates available in CEE that can be utilized in the FRAX® algorithm.

Prior to the implementation of FRAX® into national routine guidelines, reliable local fracture data need to be assessed for each CEE country to enable appropriate risk assessment and local cost–effectiveness calculation of the whole procedure.

As a next step, the implementation of FRAX® software in routine densitometry devices could be helpful in everyday diagnostic procedures in CEE countries. Through this, a consistent and reliable diagnosis of osteoporosis could be guaranteed cross-nationally in CEE. Besides, the effort for physicians would be minor because of the straightforward methodical approach of FRAX®.

The following practical remarks and questions were raised by the summit participants Is it possible that the history of nontraumatic osteoporotic fractures as well as low lumbar (beside hip) BMD values (T score of $\leq$2.5 standard deviation) could define a more precise diagnostic threshold with the aim of improving an interventional threshold for pharmacological treatment? It was agreed that including such fracture information will not yield better results.

In summary, all representatives of the CEE countries expressed interest in the use of FRAX® for fracture risk evaluation in osteoporotic patients. The discussion, however, made clear that currently, the FRAX® model cannot be implemented in CEE countries because reliable fracture data are not available to adjust the model to the special circumstances in each individual CEE country. Since the beginning of 2009, a FRAX® model based on Austrian fracture data is available. The authors suggest that in accordance with http://www.shef.ac.uk/FRAX, Austria might be used as a surrogate country for CEE countries until sufficient data for the establishment of a CEE-specific FRAX® algorithm are available.

Principles of drug selection in osteoporosis treatment in CEE countries

A range of drugs is available for the therapy of osteoporosis that significantly reduces the risk of vertebral and non-vertebral fractures [15, 19]. Most commonly used drugs are selective estrogen receptor modulators such as raloxifene; bisphosphonates such as alendronate, risedronate, ibandronate, and zoledronate; parathyroid hormone (PTH)-derived drugs such as teriparatide; and so-called dual action bone agents (DABA) including strontium ranelate. In addition, hormone replacement therapies (females, estrogen; males, testosterone) can be used [15, 19].

The decision for one or more of these therapeutic approaches is based primarily on the fracture risk of an individual patient [4, 5] but also on biochemical markers for bone turnover [6, 7]. In addition, individual patient's characteristics should be considered: Will the patients comply with a therapy? Are they able to swallow their medication or do they need intravenous application? How is their individual tolerability to a certain drug? etc.

Comments of the delegates on drug selection in CEE countries

Treatment decisions in osteoporosis should be based on a multifactorial approach Treatment decisions in osteoporosis should be based on the absolute risk of fracture (when possible by use of FRAX®) which combines the patient's clinical risk factors with BMD values. In all cases of low bone mass or low-trauma fractures, metabolic disorders as secondary causes of osteoporosis should be ruled out; however, causative management of secondary osteoporosis does not exclude the need for antifracture pharmacotherapy. In selected patients, an assessment of bone turnover rates using biochemical markers of bone turnover could possibly influence the selection of the most appropriate treatment.

General considerations on drug selection Drug selection in osteoporosis treatment should take into account the mechanism of action of the drug and the results of randomized, placebo-controlled clinical trials demonstrating the effects of a given intervention on fracture risk. Comorbidities as well as nonskeletal risks and benefits of the drug should also be considered.

Osteoporosis is a chronic disease. Therefore, long-term adherence (compliance and persistence) to the treatment is as important as effectiveness. The suitability of the drug for long-term administration and factors such as patient's preference, tolerability, and convenience should be taken into account.

Anticatabolic drugs are most appropriate in patients with high bone turnover, while anabolic drugs demonstrate efficacy irrespective of bone turnover. Anabolic treatment should be chosen particularly in patients with low bone formation or extremely low bone mass, in elderly, in cases of glucocorticoid-induced osteoporosis, or after multiple fractures where preservation of bone mass and bone architecture by antiresorptive drugs is not sufficient to reduce the high absolute risk of fracture efficiently.

Recent studies give evidence that sequential treatment with anabolic followed by anticatabolic drugs may preserve and even improve the gain in bone mass needed for long-term efficacy.

Bisphosphonates All bisphosphonates are highly effective in postmenopausal female and male patients with established osteoporosis, especially in those with high bone turnover. Presently, there is no evidence of any effect of bisphosphonates in osteopenia.

The main differences among various oral bisphosphonates relate mostly to compliance and persistence (adherence to therapy). A once-a-month schedule is better accepted by patients than once a week, which, in turn, seems to be better than a daily schedule.

Intravenous bisphosphonates (ibandronate, 3 mg every 3 months; zoledronate, 5 mg once a year) may be particularly useful in the treatment of patients with gastrointestinal disorders and patients intolerant to oral bisphosphonates, as well as patients who are chronically immobilized (as a result of vertebral or hip fractures; stroke patients), or with dementia. Once yearly zoledronic acid therapy does not only maintain bone microarchitecture but also enables sufficient bone preservation. Moreover, apart from the bone-preserving effect, zoledronic acid administered once a year guarantees high adherence to therapy.

Dual action bone agents Strontium ranelate, with its synchronous antiresorptive and pro-anabolic effects, shows antifracture efficacy in all types of osteoporotic fractures, both vertebral and nonvertebral, regardless of initial BMD or bone turnover. Moreover, a statistically significant reduction in the incidence of femoral fractures in older women with low bone mineral density can be shown.

Parathyroid hormone-derived drugs Teriparatide is a highly effective bone anabolic agent; treatment studies show a highly significant reduction of osteoporotic fractures of any type in patients with severe osteoporosis. Presently, it is the only medication which restores bone structure independently of the degree of initial disarrangement. For safety reasons, however, the duration of treatment has been restricted to 24 months. In order to maintain the achieved therapeutic effects, continuation of treatment with bisphosphonates should be considered.

In summary, drug selection should be based not only on physical (absolute risk of fractures, biochemical markers of bone turnover, etc.) but also on patient-specific (comorbidities, patient's preference, tolerability, ability to comply, etc.) factors. In addition, the mode of action of a drug should match the pathological characteristics (e.g., high/low bone turnover) of an individual patient. Specifically, anticatabolic drugs are most appropriate in patients with high bone turnover, while anabolic drugs demonstrate efficacy irrespective of bone turnover. To achieve long-term efficacy, sequential treatment with anabolic followed by anticatabolic drugs should be considered. All bisphosphonates are highly effective in postmenopausal patients with established osteoporosis; decision on oral vs. intravenous formulations as well as on the application schedule should depend on patient characteristics. DABAs are suitable for all types of fractures irrespective of BMD and bone turnover. The PTH-derived drug teriparatide is currently the only formulation which restores bone structure also in patients suffering from severe osteoporosis.

Nonpharmacological interventions in osteoporosis treatment and prophylaxis in CEE countries

Besides proper medication, a multitude of further measures have been demonstrated to reduce the risk of osteoporosis, osteoporosis-related fractures, and fall-related injuries. Physical activity, for example, has not only a positive impact on bone mineral density [23–25] but also prevents falls especially in elderly patients by increasing their balance and physical confidence [26]. Adequate intake of calcium supports the positive effect of physical activity [27] and increases bone mineral density [28]. Regular intake of vitamin D reduces the risk of falls and the fracture risk [29, 30].

Comments of the delegates on nonpharmacological interventions and prophylaxis in CEE countries

Considerations regarding vitamin D supplementation During any osteoporosis therapy, vitamin D status should be optimized (serum 25OHD >30 ng/ml in serum) for a proper antifracture effect.

Preventions of falls and hip fracture risk reduction are evidenced for vitamin D supplementation in vitamin D-

deficient patients. The recommended daily dose of vitamin D should range between 800-2,000 IU.

Patients with decreased renal function should be supplemented with activated vitamin D metabolites.

A history of kidney stones or hypercalciuria needs further evaluation before initiating vitamin D supplementation.

Other considerations Many nonspinal fractures result from a fall. Hence, each elderly patient should be asked about falls; if one or more are reported, a multidisciplinary program should be implemented.

General practitioners should provide printed educational materials with information on prophylaxis such as fall prevention, proper daily exercise, adequate lifestyle changes, etc.

Spinal dysfunction and peripheral joint pain limiting movement as well as weakening of muscles should be considered as indications for rehabilitation.

Besides vitamin D intake, calcium supplementation is the main approach used in fracture prevention and the necessary complement to osteoporosis treatment. The recommended daily dose of calcium is 500-1,500 mg.

In summary, besides calcium and vitamin D supplementation, the panel members underlined the importance of comprehensively enquiring about the medical history of patients, proper education as well as the use of multidisciplinary approaches in the prevention and treatment of osteoporosis.

Treatment benefit evaluation in CEE countries

Monitoring the effects of osteoporosis therapy informs the physician whether a certain treatment was efficient or not. Besides fracture rates, several surrogate markers are employed to evaluate the outcome of osteoporosis therapy. The most commonly used surrogate markers are sequential measurements of BMD and bone turnover markers (BTMs). Stable or increasing BMD and suppressed BTMs are associated with a reduction in fracture risk [31–34]. The available surrogate measurements of bone strength which are applied to assess the effects of osteoporosis treatment were intensively discussed by the participants.

Comments of the delegates on treatment benefit evaluation

General considerations Presently, BMD measurements are the most widely used and probably the best long-term assessment of the efficacy of antifracture treatment. Bone turnover can be monitored using BTMs (CTX, P1NP, OC). However, the usefulness of these markers in the clinical practice as a short-term (at 3 months) surrogate monitoring tool in patients treated with antiresorptives (bisphosphonates, raloxifene, hormone therapy, calcitonin) or anabolic (PTH) drugs needs to be further validated. In both BTMs and BMD measurements, precision standards and quality control by calculation of the least significant change (LSC) for the biochemical assays and BMD measurements should be taken into account for the interpretation of the individual results. Only compliant patients may be defined as "nonresponder" or "suboptimal responder" when no significant changes (according to LSC) of BMD or BTMs are observed during treatment. A patient is defined as compliant when she/he correctly takes at least 80% of the prescribed doses of the treatment in a minimal time interval of 1 year.

The most controversial point appeared to be the question whether an incident fracture is a reliable clinical endpoint for evaluation of a therapy's effectiveness. Fractures do not appear as uniform events being very heterogeneous depending on the analyzed country. On the one hand, a fracture is a stochastic event (i.e., subject to randomness) that may or may not occur in an osteoporotic patient regardless of the treatment. On the other hand, fracture prevention is the primary aim of osteoporosis treatment. However, the incident fracture rate has been defined as the primary endpoint in all relevant osteoporotic clinical trials but with potential limits when judged in a single patient. It was agreed that an incident fracture is not necessarily a treatment failure. However, if the fracture occurs a considerable time after the commencement of the treatment, the need for drug change (anticatabolic to anabolic) and specific nonpharmacological intervention (fall prevention, balance training, muscle strengthening) should be considered, if possible.

The general conclusion of all participants led to the statement that treatment benefit evaluation can be considered one of the most important factors to improve long-term antifracture efficacy. Since there are no direct tools for bone strength measurement in living patients, we are presently limited to existent surrogate ones.

Cost–effectiveness and evaluation of reimbursement policies in CEE countries

As a chronic disease that in many cases is accompanied by limiting complications and consequences, osteoporosis is a very treatment- and, hence, cost-intensive condition. Considering also the high prevalence of this disease, the burden imposed by osteoporosis on health care systems is enormous. Especially in countries with limited resources and health care budgets, the decision taken on diagnostic and therapeutic measures to prevent or treat osteoporosis has to be based not only on therapeutic but also on economic considerations. Health-economy analyses that

evaluate the cost/benefit ratio of a certain therapy can support the efficient allocation of such limited resources. Indeed, economic evaluations have been performed to compare distinct treatment strategies in osteoporosis [35–37]. However, to realistically represent the cost/benefit of these therapies in a certain area or country, detailed local data on epidemiology, type of treatment, treatment expenses, success rates, etc. have to be incorporated into the evaluation.

Difficult and heterogeneous economic situation in CEE Due to historical developments, the economic situation in CEE countries shows large differences also regarding budgets available for health care. Besides countries with sufficient financial means for health care, there are also a considerable number of countries where resources are limited. Cost–effectiveness analyses provide important information about the value of different treatment options. Their outcome assists decision makers who try to equitably allocate constrained resources in order to achieve maximum health care benefits. By definition, cost–effectiveness analyses compare the costs and health effects of an intervention to assess whether it is worth doing from an economical perspective. From an ethical point of view, economically dealing with resources is a must.

Data required for cost–effectiveness analyses are not available With respect to osteoporosis and cost–effectiveness, reliable epidemiological data and the exact cost of osteoporosis and fracture treatments are necessary as well as data on normal life expectancy and gross national product. While in Poland, the cost–effectiveness of alendronate and raloxifene (once a day) as well as ibandronate (once a month) therapies for postmenopausal osteoporosis were evidenced and published [38], in most other CEE countries, the cost of osteoporosis treatment is not available. One of the reasons that should be considered in this context is that registers for hip fractures and other fractures are far from being satisfactory in this region.

Reimbursement strategies are very heterogeneous in distinct CEE countries Only in some CEE countries do uniform reimbursement criteria exist. In general, however, reimbursement of diagnostic procedures, prevention, and therapy of osteoporosis varies considerably among countries as well as factors influencing reimbursement policies. In fact, there are currently no recommendations on how and to what extent reimbursement policies in CEE countries should be influenced by cost–effectiveness analyses. In addition, in the majority of CEE countries, medical communities are not involved in cost–effectiveness evaluation.

Which substances are reimbursed in CEE In the majority (>50%) of CEE countries, alendronate, risedronate, ibandronate, zoledronic acid, strontium ranelate, and teriparatide/rh PTH are reimbursed; however, while in some countries, therapy costs are fully covered, in other countries, costs are reimbursed only partially. Raloxifene is not reimbursed at all in some countries.

Recommendations for the future In the long run, the main approach should focus on (a) the development of CEE-specific FRAX® algorithms to guarantee reliable diagnosis, thereby increasing the efficacy of therapeutic measures, and (b) country-specific cost–effectiveness models to facilitate calculation of regional therapy costs. Such models of the cost–effectiveness of antifracture therapies would enable the assessment and comparison of different drugs (alendronate, ibandronate, risedronate, raloxifene, strontium ranelate, zoledronic acid), different screening strategies (BMD, BTM, DXA), or patients of different ages and sex.

In summary, the CEE delegates pointed out the heterogeneous economic situations in CEE countries and emphasized that country-specific health-economy analyses are required to shed light on the cost–effectiveness of local osteoporosis therapies. However, the data required to conduct such analyses (epidemiology data, exact costs of therapies, etc.) are not available. In addition, reimbursement strategies vary considerably between countries, making an objective evaluation of local situations even more difficult. As a future perspective, they suggested that diagnosis and therapy of osteoporosis should be based on the concerted use of CEE-specific FRAX® algorithms and local cost–effectiveness data.

Overall summary and outlook

The major aim of the "2nd summit on Osteoporosis—CEE" was to identify and discuss diagnostic, prophylactic, and therapeutic measures used in CEE countries to prevent and treat osteoporosis [39]. Based on such information, issues concerning the management of osteoporosis in these countries should then be identified to provide the basis for the development of suitable support and development strategies.

It was agreed that a proper diagnosis especially of the patient's fracture risk is the absolute prerequisite for the decision on an adequate and successful therapy. To facilitate a simple but reliable diagnose of the fracture risk, all representatives of the CEE countries argued for the implementation of the computer-based tool FRAX® for fracture risk evaluation in CEE. For this, information on the local epidemiology of fracture and death rates is required.

Such data, however, are currently not available for most countries in CEE. Therefore, the first step toward FRAX® implementation would be to develop a strategy on how such information can be collected most efficiently in CEE countries. Until sufficient local epidemiology data for the establishment of CEE-specific FRAX® algorithms are available, the Austrian FRAX® model was proposed as a surrogate model for CEE.

Drug selection should be based on physical parameters (absolute risk of fractures, biochemical markers of bone turnover, etc.) as well as on patient-specific factors (comorbidities, patient's preference, tolerability, ability to comply, etc.). Such patient characteristics should also be considered when deciding on the way of administration (oral vs. intravenous) and the administration schedule (daily up to once a year). The most commonly used therapies are bisphosphonates, DABA, and PTH-derived formulations. In addition to such medication-based treatments, calcium and vitamin D supplementation were discussed to be vital for a successful therapy as well as measures such as comprehensively enquiring about the patient's medical history, proper education, and, in general, the use of multidisciplinary therapeutic approaches. For evaluation of the benefit of a specific osteoporosis treatment, no direct tools are currently available; therefore, surrogate ones have to be employed.

Finally, the CEE delegates described the very heterogeneous economic situations in the different CEE countries and emphasized that country-specific health-economy analyses would be required to shed light on the cost–effectiveness of local osteoporosis therapies. For such studies, however, epidemiology data, data on the exact costs of therapies, etc. have first to be evaluated in each country. As soon as available, the combined use of CEE-specific FRAX® algorithms and local cost–effectiveness data would then allow an adequate and economical management of osteoporosis.

In conclusion, the lively discussion and exchange of information at the "2nd Summit on Osteoporosis—CEE" in November 2008 made clear that this meeting is a very helpful and authentic platform to identify issues and needs regarding the diagnosis and therapy of osteoporosis as well as the cost–effectiveness of osteoporosis management in CEE countries. Based on the information gained, the "3rd Summit on Osteoporosis—CEE" in November 2009 will then focus on the development of answers and strategies to resolve the identified issues.

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ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Steven R. Cummings, M.D., Javier San Martin, M.D., Michael R. McClung, M.D., Ethel S. Siris, M.D., Richard Eastell, M.D., Ian R. Reid, M.D., Pierre Delmas, M.D., Ph.D., Holly B. Zoog, Ph.D., Matt Austin, M.S., Andrea Wang, M.A., Stepan Kutilek, M.D., Silvano Adami, M.D., Ph.D., Jose Zanchetta, M.D., Cesar Libanati, M.D., Suresh Siddhanti, Ph.D., and Claus Christiansen, M.D., for the FREEDOM Trial*

ABSTRACT

BACKGROUND

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Given its unique actions, denosumab may be useful in the treatment of osteoporosis.

METHODS

We enrolled 7868 women between the ages of 60 and 90 years who had a bone mineral density T score of less than −2.5 but not less than −4.0 at the lumbar spine or total hip. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary end point was new vertebral fracture. Secondary end points included nonvertebral and hip fractures.

RESULTS

As compared with placebo, denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group, versus 7.2% in the placebo group (risk ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.41; P<0.001) — a relative decrease of 68%. Denosumab reduced the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group, versus 1.2% in the placebo group (hazard ratio, 0.60; 95% CI, 0.37 to 0.97; P=0.04) — a relative decrease of 40%. Denosumab also reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, versus 8.0% in the placebo group (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) — a relative decrease of 20%. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of denosumab.

CONCLUSIONS

Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis. (ClinicalTrials.gov number, NCT00089791.)

From the San Francisco Coordinating Center, California Pacific Medical Center Research Institute and University of California, San Francisco, San Francisco (S.R.C.); Amgen, Thousand Oaks, CA (J.S.M., H.B.Z., M.A., A.W., C.L., S.S.); Oregon Osteoporosis Center, Portland (M.R.M.); Columbia University Medical Center, New York (E.S.S.); University of Sheffield, Sheffield, United Kingdom (R.E.); University of Auckland, Auckland, New Zealand (I.R.R.); Université de Lyon and INSERM Research Unit 831, Lyon, France (P.D.); the Center for Clinical and Basic Research, Pardubice, Czech Republic (S.K.); University of Verona, Verona, Italy (S.A.); Instituto de Investigaciones Metabolicas and University of Salvador, Buenos Aires, Argentina (J.Z.); and the Center for Clinical and Basic Research, Ballerup, Denmark (C.C.). Address reprint requests to Dr. Cummings at 185 Berry St. Lobby 4, Suite 5700, San Francisco, CA 94107, or at hglicklandes@sfcc-cpmc.net.

*Investigators for the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial are listed in the Appendix.

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Fractures are a major cause of disability and health care costs.[1,2] The use of denosumab is a novel approach to fracture prevention. It is a fully human monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL), a cytokine that is essential for the formation, function, and survival of osteoclasts.[3] By binding RANKL, denosumab prevents the interaction of RANKL with its receptor, RANK, on osteoclasts and osteoclast precursors and reversibly inhibits osteoclast-mediated bone resorption.[4]

In previous trials, the subcutaneous administration of 60 mg of denosumab every 6 months reduced bone turnover and increased bone mineral density.[5-8] We tested the effect of denosumab on the risk of fracture in postmenopausal women with osteoporosis.

METHODS

STUDY DESIGN

Our study, called Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM), was an international, randomized, placebo-controlled trial. Subjects were randomly assigned to receive subcutaneous injections of either 60 mg of denosumab or placebo at study sites every 6 months for 36 months. Randomization was stratified according to 5-year age groups.

SUBJECTS

Women between the ages of 60 and 90 years with a bone mineral density T score of less than −2.5 at the lumbar spine or total hip were eligible for inclusion. Women were excluded if they had conditions that influence bone metabolism or had taken oral bisphosphonates for more than 3 years. If they had taken bisphosphonates for less than 3 years, they were eligible after 12 months without treatment. Women were also excluded if they had used intravenous bisphosphonates, fluoride, or strontium for osteoporosis within the past 5 years; or parathyroid hormone or its derivatives, corticosteroids, systemic hormone-replacement therapy, selective estrogen-receptor modulators, or tibolone, calcitonin, or calcitriol within 6 weeks before study enrollment.

Although consensus conferences have not specified a permissible risk of fracture for placebo-controlled trials,[9,10] women were excluded if they had a bone mineral density T score of less than −4.0 at the lumbar spine or total hip or any severe (or more than two moderate) prevalent vertebral fractures. As part of the consent process, potential subjects were informed about alternative treatments for osteoporosis. All women received daily supplements containing at least 1000 mg of calcium. Women were excluded if they had a serum 25-hydroxyvitamin D level of less than 12 ng per milliliter. Subjects with a baseline 25-hydroxyvitamin D level of 12 to 20 ng per milliliter were given at least 800 IU of vitamin D daily, and those with a baseline level above 20 ng per milliliter were given at least 400 IU daily. If total hip bone mineral density decreased by more than 7% during a 12-month period or by 10% or more during the study or if the T score dropped below −4.0, the subject was again counseled by the local study clinician about using alternative treatments in lieu of continuing to participate in the study. The trial and consent process were approved by the institutional review boards and ethics committees overseeing the study sites in the United States and other countries; 139 of 142 boards that reviewed the protocol approved it.

ASSESSMENTS OF EFFICACY

Lateral spine radiographs were taken annually and assessed for new vertebral fractures by a semiquantitative grading scale[11] at the central imaging center (Synarc). A prevalent fracture was defined as a vertebral body with a semiquantitative grade of 1 or more. A new vertebral fracture was defined as an increase of at least 1 grade in a vertebral body that was normal at baseline. Secondary end points were the time to the first nonvertebral fracture and the time to the first hip fracture. Fractures of the skull, face, mandible, metacarpals, fingers, or toes were excluded because they are not associated with decreased bone mineral density; pathologic fractures and those that were associated with severe trauma (defined as a fall from a height higher than a stool, chair, or first rung of a ladder or severe trauma other than a fall) were also excluded.[12] Clinical fractures were confirmed by diagnostic imaging or a radiologist's report.

Bone mineral density as evaluated on dual-energy x-ray absorptiometry was measured at baseline and then annually at the hip and after 36 months at the lumbar spine. Bone mineral density of both sites was measured at baseline and at 1, 6, 12, 24, and 36 months in 441 subjects. Concentrations of two markers of bone turnover were measured in 160 subjects from fasting serum samples collected before the injection on day 1, at

Table 1. Baseline Characteristics of the Subjects.*

Variable	Denosumab (N=3902)	Placebo (N=3906)
Age		
Mean — yr	72.3±5.2	72.3±5.2
Group — no. (%)		
<70 yr	1030 (26.4)	1028 (26.3)
70–74 yr	1637 (42.0)	1642 (42.0)
≥75 yr	1235 (31.7)	1236 (31.6)
Body-mass index†	26.0±4.1	26.0±4.2
Region — no. (%)‡		
Western Europe	1761 (44.8)	1773 (45.1)
Eastern Europe	1374 (34.9)	1355 (34.4)
Latin America	472 (12.0)	462 (11.7)
North America	282 (7.2)	297 (7.5)
Australia and New Zealand	44 (1.1)	48 (1.2)
T score		
Lumbar spine	−2.82±0.70	−2.84±0.69
Total hip	−1.89±0.81	−1.91±0.81
Femoral neck	−2.15±0.72	−2.17±0.71
Prevalent vertebral fracture — no. (%)		
Yes	929 (23.8)	915 (23.4)
No	2864 (73.4)	2854 (73.1)
Unreadable or missing data	109 (2.8)	137 (3.5)
Serum 25-hydroxyvitamin D — ng/ml§	23.1±11.7	22.9±11.3

* Plus–minus values are means ±SD. A total of 60 subjects at one center (31 in the denosumab group and 29 in the placebo group) were excluded from all analyses because of issues with respect to study procedures and the reliability of data.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Percentages for region are based on all subjects enrolled in the study: 3933 in the denosumab group and 3935 in the placebo group.

§ Subjects with outlier values of more than 200 ng per milliliter were excluded from this analysis.

1 month after the baseline injection, and before injections at 6, 12, 24, and 36 months. Bone-turnover marker serum C-telopeptide of type I collagen was evaluated with the use of enzyme-linked immunosorbent assay (ELISA) (Nordic Bioscience Diagnostics A/S), and intact serum procollagen type I N-terminal propeptide (PINP) was evaluated with the use of radioimmunoassay (Orion Diagnostica Oy).

ADVERSE EVENTS

Physicians at study sites reported adverse events that were coded as preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA) system. All deaths and serious adverse events that were possibly related to cardiovascular disease were adjudicated by a committee of cardiologists using predefined criteria. A committee of experts reviewed reported events that met a broad range of MedDRA terms that might represent osteonecrosis of the jaw, defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after diagnosis.[13] Study investigators clinically assessed the healing of nonvertebral fractures within 6 months after their occurrence. A positive result on hypocalcemia testing was defined as an albumin-adjusted calcium level of less than 8.0 mg per deciliter (2.0 mmol per liter) in fasting specimens drawn just before injection of the study drug. Denosumab-specific antibodies were also assessed in those samples.

STUDY OVERSIGHT

A steering committee, consisting of a majority of investigators who were not employed by study sponsor Amgen, planned the analyses for the manuscript before the unblinding of data, and one member wrote the first draft of the manuscript. The committee members approved the manuscript for publication and vouch for the completeness and accuracy of the data. Analyses were performed by the sponsor and confirmed by an analyst at the San Francisco Coordinating Center. The authors received all analyses that they requested. The sponsor designed the protocol with advice from external investigators and was responsible for the management and quality control of data collected by the clinical sites. A data and safety monitoring committee reviewed unblinded data at least twice yearly.

STATISTICAL ANALYSIS

The study had a power of more than 99% to detect a 45% reduction in the incidence of new vertebral fractures and to detect a 40% reduction in the risk of any nonvertebral fracture and a power of 91% to detect a 40% reduction in the risk of hip fracture. These estimates were based on the assumption that the annual fracture rate in the placebo group over a 36-month period would be 4.0% for vertebral fractures, 3.3% for nonvertebral fractures, and 1.0% for hip fractures.

Analyses of efficacy were based on the intention-to-treat principle. To adjust for multiplicity and maintain the overall significance level at 0.05,

Table 2. Effect of Denosumab on the Risk of Fracture at 36 Months.*

Outcome	Denosumab	Placebo	Difference in Rates (95% CI)	Relative Risk or Hazard Ratio (95% CI)†	P Value
	no. (%)				
Primary end point					
New vertebral fracture	86 (2.3)	264 (7.2)	4.8 (3.9 to 5.8)	0.32 (0.26 to 0.41)	<0.001
Secondary end points					
Nonvertebral fracture‡	238 (6.5)	293 (8.0)	1.5 (0.3 to 2.7)	0.80 (0.67 to 0.95)	0.01
Hip fracture	26 (0.7)	43 (1.2)	0.3 (–0.1 to 0.7)	0.60 (0.37 to 0.97)	0.04
Other fracture end points					
New clinical vertebral fracture	29 (0.8)	92 (2.6)	1.7 (1.1 to 2.3)	0.31 (0.20 to 0.47)	<0.001
Multiple (≥2) new vertebral fractures	23 (0.6)	59 (1.6)	1.0 (0.5 to 1.5)	0.39 (0.24 to 0.63)	<0.001

* The percentages of new and multiple new vertebral fractures are calculated for 3702 subjects in the denosumab group and 3691 in the placebo group who underwent spinal radiography at baseline and during at least one visit after baseline. The percentages of nonvertebral, hip, and new clinical vertebral fractures are cumulative Kaplan–Meier estimates for 3902 subjects in the denosumab group and 3906 in the placebo group.

† Risk ratios are based on the Mantel–Haenszel method with adjustment for the age-stratification variable for vertebral fractures. Hazard ratios are based on the Cox proportional-hazards model with adjustment for the age-stratification variable for nonvertebral, hip, and clinical vertebral fractures.

‡ A total of 28 subjects (13 in the denosumab group and 15 in the placebo group) had nonvertebral fractures associated with severe trauma and were not included in the analysis.

the primary end point of new vertebral fracture was required to achieve significance before the next end points in the sequence (nonvertebral fracture and hip fracture) could be tested. Analyses regarding vertebral fractures included all subjects who had at least one follow-up radiograph.

The effect of treatment on the risk of new vertebral fracture was analyzed with the use of a logistic-regression model with adjustment for age strata. An age-stratified Cox proportional-hazards model was used to compare the two study groups for the secondary end points. Score tests were used to calculate P values in each model.[14,15] Subjects who were lost to follow-up or withdrew before having a fracture event had their last known fracture status carried forward. Radiographically defined vertebral fractures were analyzed by cumulative incidence and secondary end points by time-to-event analysis with the use of Kaplan–Meier methods. The absolute risk reduction between study groups was computed as the difference in incidence at 36 months for the primary end point and the difference in the Kaplan–Meier estimates at 36 months for the secondary end points with the use of a weighted average across the age strata. Analyses of changes in bone mineral density included all subjects who had at least one follow-up measurement at or before the time point under consideration. Missing values were imputed by carrying forward the last observation.

Safety analyses included all subjects who received at least one dose of a study drug. Analyses of adverse and serious adverse events of cancer, infection, specific cardiovascular events, and potential adverse effects of potent antiresorptive therapies (including osteonecrosis of the jaw, delayed fracture healing, femoral-shaft fracture, hypocalcemia, and atrial fibrillation) were specified in advance. Preferred terms similar to eczema were combined as eczema, and erysipelas was included with cellulitis. To adjust for multiple comparisons for numerous reports of adverse events, we specified in advance to report MedDRA preferred terms of adverse events that occurred in at least 2% of subjects in either study group with a P value of 0.05 or less and serious adverse events that occurred in at least 0.1% of subjects in either group with a P value of 0.01 or less.

RESULTS

SUBJECTS

A total of 7868 women were enrolled in the study, 3933 in the denosumab group and 3935 in the pla-

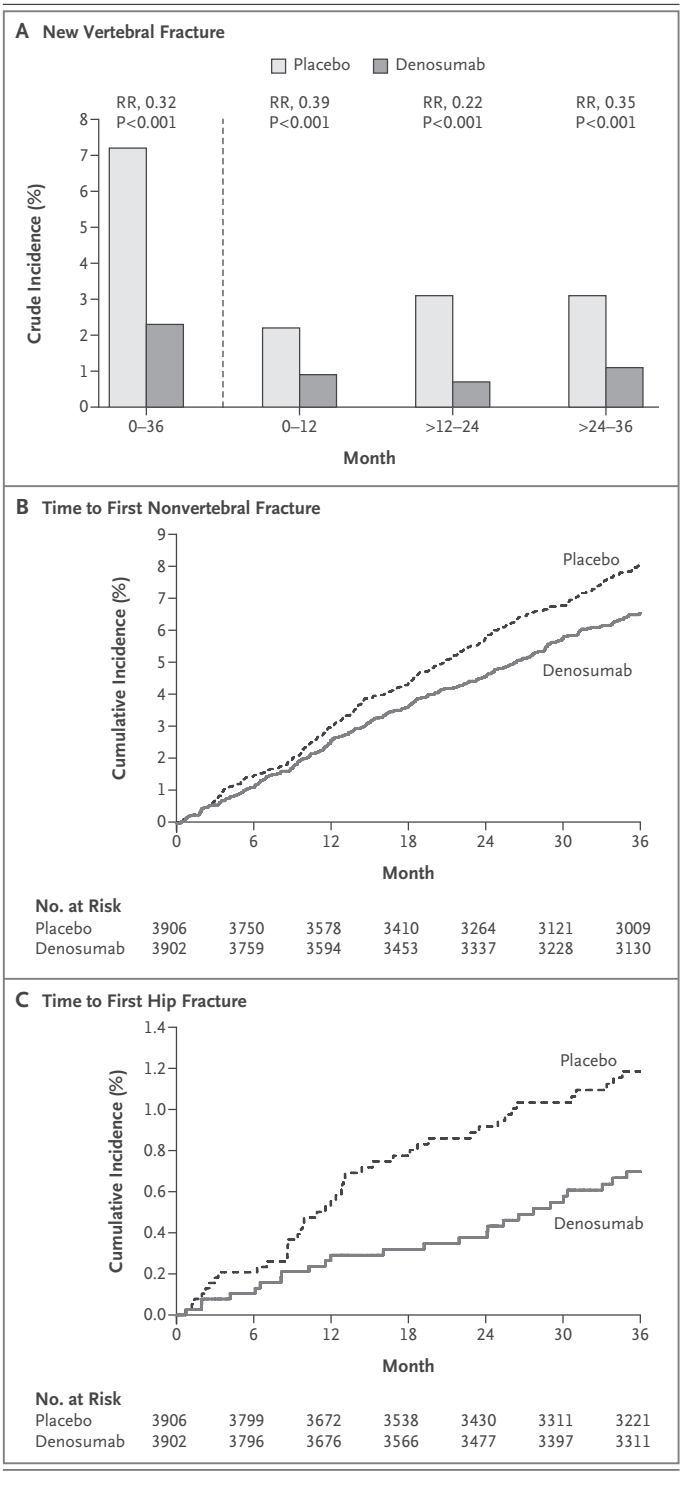

Figure 1. Incidence of New Vertebral, Nonvertebral, and Hip Fractures.

The primary end point was the incidence of new vertebral fractures at 36 months (Panel A, left), which is shown for each study year (Panel A, right). Risk ratios (RRs) are for subjects in the group receiving denosumab, as compared with those receiving placebo. Kaplan–Meier curves of the time to the first nonvertebral fracture (Panel B) and the first hip fracture (Panel C) were determined on the basis of subjects who did not have a fracture or who did not leave the study before the time point of interest. The subjects at risk at 36 months included all those who completed end-of-study visits at or after the start of the window for the 36-month visit.

cebo group. Of these subjects, 60 (31 in the denosumab group and 29 in the placebo group) were excluded from all analyses because the participation of their study center was halted owing to issues related to study procedures and the reliability of data. Baseline characteristics were similar between the two study groups (Table 1). The mean bone mineral density T scores were –2.8 at the lumbar spine, –1.9 at the total hip, and –2.2 at the femoral neck. About 24% of women had a vertebral fracture at baseline. Of 7868 subjects, 6478 (82%) completed 36 months of study and 5979 (76%) received all injections.

FRACTURES, BONE DENSITY, AND MARKERS OF BONE TURNOVER

The calculations of percentages of new and multiple new vertebral fractures were based on the number of subjects who underwent spinal radiography at baseline and during at least one visit after baseline. The 36-month incidence of new radiographic vertebral fracture was 2.3% (86 of 3702 subjects) in the denosumab group and 7.2% (264 of 3691 subjects) in the placebo group, representing a 68% reduction in relative risk (P<0.001) (Table 2). The reduction in risk was similar during each year of the trial (Fig. 1A). There were similar reductions in clinically diagnosed vertebral fractures (69%) and multiple new vertebral fractures (61%, P<0.001 for both comparisons) (Table 2).

The calculations of cumulative incidences of nonvertebral, hip, and new clinical vertebral fractures were based on Kaplan–Meier estimates of a 36-month cumulative incidence in 3902 subjects in the denosumab group and 3906 in the placebo group. Denosumab reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, as compared with 8.0% in the placebo group (hazard ratio, 0.80; 95% confidence interval [CI], 0.67 to 0.95; P=0.01) —

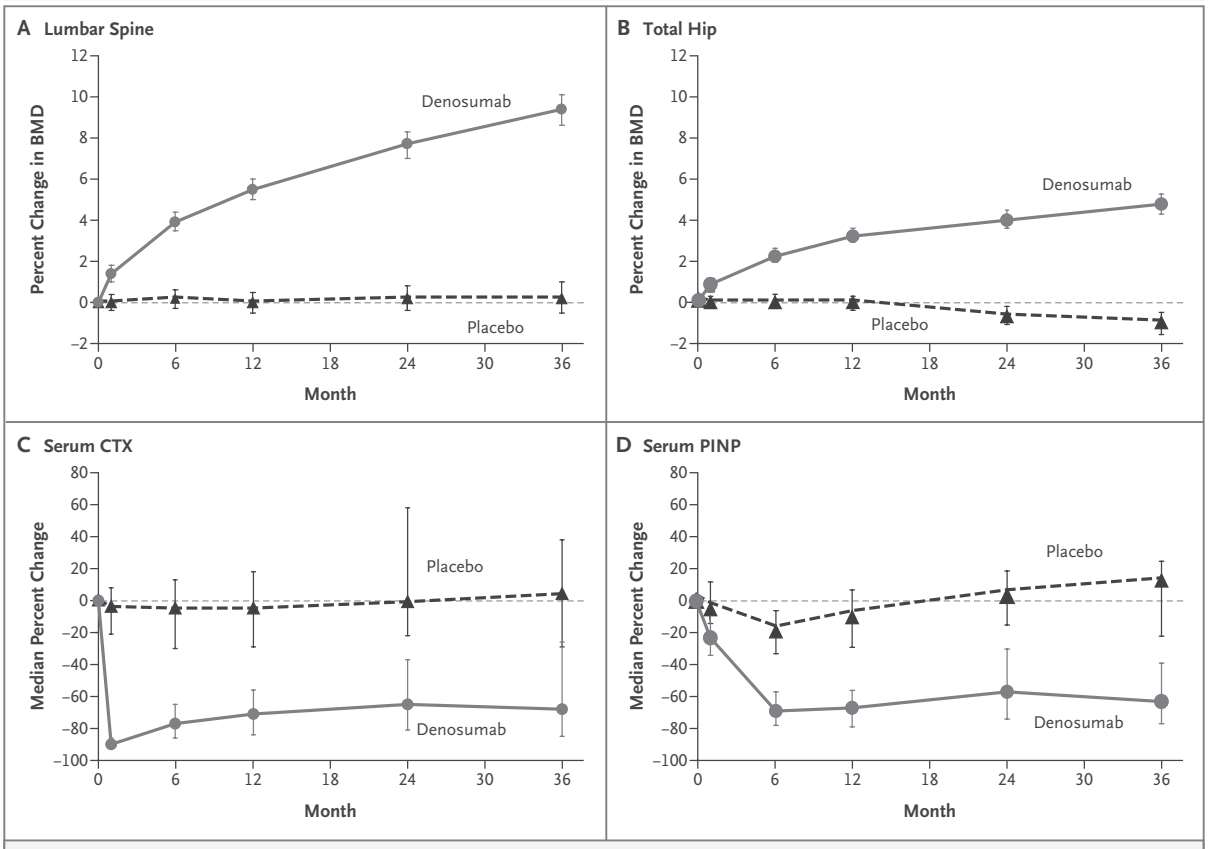

Figure 2. Percent Changes in Bone Mineral Density and Biochemical Markers of Bone Turnover.

Changes in mean bone mineral density (BMD) at the lumbar spine (Panel A) and total hip (Panel B) are shown for 441 subjects who were included in a substudy of measurements of bone mineral density. As compared with subjects in the placebo group, subjects in the denosumab group had a relative increase of 9.2% in bone mineral density at the lumbar spine and 6.0% at the total hip. Changes in mean values for serum C-telopeptide of type I collagen (CTX) (Panel C) and serum procollagen type I N-terminal propeptide (PINP) (Panel D) are shown for 160 subjects who were included in a substudy of bone-turnover markers. P<0.001 for all between-group comparisons at all time points on the basis of analysis-of-covariance (ANCOVA) models. For bone mineral density, the comparisons were adjusted for study group, baseline bone mineral density, type of machine used to analyze bone mineral density, and interaction between the type of machine and the baseline bone mineral density; for CTX and PINP, the comparisons were calculated with the use of the Wilcoxon rank-sum test.

a 20% relative reduction (Table 2 and Fig. 1B). Denosumab also decreased the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group, versus 1.2% in the placebo group (hazard ratio, 0.60; 95% CI, 0.37 to 0.97; P=0.04) — a 40% relative reduction (Table 2 and Fig. 1C).

After 36 months, denosumab was associated with a relative increase in bone mineral density of 9.2% (95% CI, 8.2 to 10.1) at the lumbar spine and 6.0% (95% CI, 5.2 to 6.7) at the total hip, as compared with placebo (Fig. 2). As compared with placebo, denosumab decreased serum C-telopeptide levels by 86% at 1 month, by 72% before treatment was administered at 6 months, and by 72% at 36 months. Levels of PINP, a marker of bone formation, were 18%, 50%, and 76% below those in the placebo group at the same time points.

ADVERSE EVENTS

There were no significant differences between subjects who received denosumab and those who received placebo in the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events (Table 3). Similarly, there were no significant differences in the overall incidence of cancer, cardio-

Table 3. Adverse Events.*

Event	Denosumab (N=3886)	Placebo (N=3876)	P Value†
	no. (%)		
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of a study drug	192 (4.9)	202 (5.2)	0.55
Adverse events			
Infection	2055 (52.9)	2108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcemia	0	3 (0.1)	0.08
Osteonecrosis of the jaw	0	0	NA
Serious adverse events			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	178 (4.6)	0.74
Stroke	56 (1.4)	54 (1.4)	0.89
Coronary heart disease	47 (1.2)	39 (1.0)	0.41
Peripheral vascular disease	31 (0.8)	30 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Adverse events occurring in at least 2% of subjects‡			
Eczema	118 (3.0)	65 (1.7)	<0.001
Falling§	175 (4.5)	219 (5.7)	0.02
Flatulence	84 (2.2)	53 (1.4)	0.008
Serious adverse events occurring in at least 0.1% of subjects¶			
Cellulitis (including erysipelas)	12 (0.3)	1 (<0.1)	0.002
Concussion	1 (<0.1)	11 (0.3)	0.004

* NA denotes not applicable.
† P values are based on the log-rank test, except for between-group comparisons of deaths and cardiovascular events, which were based on the Cox proportional-hazards model with adjustment for the baseline cardiovascular risk score.
‡ P≤0.05 for the between-group comparison. Among terms listed in the *Medical Dictionary for Regulatory Activities* (MedDRA), the incidence of adverse events corresponding to 58 MedDRA-preferred terms was at least 2% in either study group.
§ This category excludes falls that occurred on the same day as a fracture.
¶ P≤0.01 for the between-group comparison. There were 152 MedDRA-preferred terms of serious adverse events that had an incidence of at least 0.1% in either group.

vascular events, or either adverse or serious adverse events of infection. Four cases of opportunistic infections were reported in the denosumab group and three in the placebo group. Seventy subjects (1.8%) died in the denosumab group and 90 (2.3%) in the placebo group (P=0.08).

No cases of osteonecrosis of the jaw occurred in either group. Delayed fracture healing was reported for two subjects in the denosumab group and four subjects in the placebo group, and one case of nonunion of a humerus fracture was reported in the placebo group. There were no fractures of the femoral shaft in the denosumab group and three such fractures in the placebo group (0.1%). There were no reports of hypocalcemia in the denosumab group and three events (0.1%) in the placebo group. Decreases in serum calcium to levels below 8.0 mg per deciliter occurred in four subjects in the denosumab group and five in the placebo group. Local reactions after injection of a study drug occurred in 33 subjects (0.8%) in the denosumab group and 26 subjects (0.7%) in the placebo group. Neutralizing antibodies to denosumab did not develop in any of the subjects.

Eczema was reported in 3.0% of subjects in the denosumab group and 1.7% in the placebo group (P<0.001). Falls that were not associated with a fracture were reported in 4.5% of subjects in the denosumab group and 5.7% in the placebo group (P=0.02). Flatulence was reported more frequently in the denosumab group (2.2%) than in the placebo group (1.4%, P=0.008). Twelve subjects (0.3%) in the denosumab group reported serious adverse events of cellulitis, as compared with one subject (<0.1%) in the placebo group (P=0.002). There were no significant differences in the overall incidence of adverse events of cellulitis, with 47 (1.2%) in the denosumab group and 36 (0.9%) in the placebo group.

DISCUSSION

In postmenopausal women with osteoporosis, the subcutaneous administration of 60 mg of denosumab every 6 months for 36 months significantly reduced the risk of vertebral and nonvertebral fractures and the risk of hip fracture. The reduction in the risk of vertebral fracture was similar in the first and subsequent years and for both clinically diagnosed and multiple vertebral fractures.

Denosumab prevents the interaction of RANKL with RANK, its receptor, on osteoclasts and their precursors, thereby blocking the formation, function, and survival of osteoclasts.[3] In contrast, bisphosphonates chemically bind to calcium hydroxy-

apatite in bone; they decrease bone resorption by blocking the function and survival, but not the formation, of osteoclasts.[16]

The magnitude of the risk reduction of vertebral fracture with denosumab was similar to that reported for intravenously administered zoledronic acid and appears to be greater than reductions reported for oral osteoporosis agents.[17-20] For nonvertebral fractures, the risk reduction with denosumab was similar to those reported for alendronate, risedronate, and zoledronic acid.[17,20,21] However, comparisons of efficacy are limited because there has been no head-to-head trial comparing rates of fracture reduction associated with denosumab and bisphosphonates. In addition, trials have included various subgroups of nonvertebral fractures,[22-24] and study populations have varied. At least 50% of patients stop bisphosphonate treatment within 1 year after receiving a prescription for an oral agent.[25] Twice-yearly subcutaneous injections might improve adherence.

During 36 months of treatment, denosumab increased bone mineral density at the lumbar spine by about 9% and at the total hip by about 6%. A separate 12-month trial showed that denosumab increased bone mineral density significantly more than alendronate at the total hip and spine.[26]

Denosumab reduced bone resorption by a median of 86% at 1 month, which is greater than the reductions seen with other antiresorptive drugs.[21,27] In retrospective analyses from trials of antiresorptive drugs, the magnitude of the decrease in bone-turnover markers was shown to be associated with the reduction in fracture risk.[28] Whether this finding also applies to denosumab requires further study. Impaired fracture healing and osteonecrosis of the jaw have been reported with bisphosphonate therapy in postmarketing case reports, raising concern that these conditions may be caused by decreased bone resorption. No significant adverse effects on fracture healing and no cases of osteonecrosis of the jaw occurred in our study. There have also been reports of cases of unusual fractures of the femoral shaft associated with long-term administration of alendronate. No fractures of the femoral shaft occurred in the denosumab group during 36 months of study. Patients in the trial are continuing to receive denosumab, to assess the potential effects of long-term treatment, including fractures, fracture healing, infections, and cancer.

RANKL and RANK are members of the tumor necrosis factor superfamily that are expressed by a variety of lymphoid cells.[29] It has been theorized that the inhibition of RANKL might increase the risk of cancer or infection.[30] In this trial, there was no significant difference in the incidence of cancer or in the overall incidence of infection, serious adverse events of infection, or opportunistic infection during 36 months of treatment; longer follow-up is under way. An increased incidence of hospitalization for cellulitis was observed in subjects who were treated with denosumab; however, there was no significant difference in the overall incidence of cellulitis between the two groups.

Before a new treatment for osteoporosis can be approved, the Food and Drug Administration and the European Committee for Medicinal Products for Human Use have required that placebo-controlled trials be conducted for 3 years in subjects with osteoporosis. Some observers have raised concern about the enrollment of subjects with osteoporosis in placebo-controlled trials, although there is no consensus about an allowable risk for inclusion.[9,10] To reduce the risk for control subjects, trials involving subjects at reduced risk for osteoporosis might be considered. However, the effects of treatment on the risk of nonvertebral fracture in women with a bone mineral density T score above –2.5 may be weaker and not applicable to women with osteoporosis.[18,19,31] In addition, although shorter trials have been considered,[10] the results may be misleading because treatments may have greater efficacy for vertebral fracture in the first year than in subsequent years.[32-35]

In conclusion, denosumab offers an alternative approach to the treatment of osteoporosis by decreasing bone resorption and increasing bone mineral density through the inhibition of RANKL. Denosumab was associated with a significant reduction in the risk of vertebral, hip, and nonvertebral fractures in postmenopausal women with osteoporosis.

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APPENDIX

Investigators for the FREEDOM trial are as follows. **Steering Committee:** S. Cummings (chair), C. Christiansen, P. Delmas, R. Eastell, M. McClung, I. Reid, E. Siris. **Study Investigators:** *United States*: K. Aqua, E. Lee, E. Boling, M. Bolognese, F. Burch, S. Cohen, D. Fiske, C. Petit, M. Pierson, K. Garrison, E. Gallup, H. Geisberg, D. Hassman, D. Helfrich, K. Krohn, E. Cuevas, W. Larson, J. Seiler, S. Lederman, M. Lewiecki, D. MacCarter, M. McClung, P. Miller, A. Moffett, Jr., C. Recknor, J. Simon, R. Trapp, G. Woodson III, H. Bone, T. Murtaugh, J. Ruckle, R. Wasnich, C. Gallagher, G. Dhillon, R. Feldman, G. Pennington, P. Saxe, C. Goldberg, K. Rogers, M. Keller, M. Swor, A. Rosen, M. Stjernholm; *Canada*: J. Adachi, J. Brown, R. Faraawi, D. Kendler, R. Kremer, W. Olszynski, C.K. Yuen, R. McKendry, J. Boudreau; *Argentina*: Z. Man, J. Zanchetta, C. Mautalen; *Brazil*: L. de Gregorio, S. Eis, S. Radominski, N. da Silva, L. Griz, J. Provenza, C. Zerbini; *Mexico*: P. García-Hernández, M. Araujo-Arias, E. Bueno, A. Fuentes-Cantu, M. Perez, J. Balderas-Acata, H. Avila-Armengol, M. de la Peña-Rodríguez; *Australia*: G. Nicholson, P. Ebeling, P. Sambrook, M. Hooper, J. Prins, A. Russell; *New Zealand*: I. Reid, N. Gilchrist; *Austria*: E. Preisinger, H. Resch, A. Fahrleitner-Pammer, J. Huber, S. Kudlacek; *Belgium*: J.-Y. Reginster, J.-M. Kaufman, S. Boonen, J.-J. Body, J.-P. Devogelaer; *Denmark*: C. Tegibjearg, R. Juel, P. Alexandersen, H.C. Hoeck, J.-E. Jensen; *Finland*: M. Välimäki, J. Salmi; *France*: P. Delmas, P. Fardellone, G. Weryha, C.-L. Benhamou, Y. Maugars, C. Roux; *Germany*: H.-D. Stahl, U. Blome-Henning, B. Lochman, U. Kopsch, A. Roitenberg; *Italy*: S. Adami, M. Brandi, S. Minisola, G. Bianchi, L. Sinigaglia, B. Frediani, R. Marcolongo, C. Fiore, R. Nuti, G. Realdi; *the Netherlands*: B. Dijkmans, R. Laan, G. Bruyn, A. Deijl, E. Meesters, W. Lems, A. Verhage, V. van de Walle; *Norway*: J. Halse, A. Hoiseth, U. Syversen, J. Stakkestad; *Spain*: J. Minguella, E. Mola, M. Torres, J. Gómez, F. Hawkins, J. Román, J. Alvaro-Gracia, J. Del Pino, S. Palacios; *Sweden*: Ö. Ljunggren, G. Toss, G. Samsioe, D. Mellström, J. Löfgren, O. Törring; *Switzerland*: K. Lippuner, M.-A. Krieg, D. Uebelhart; *United Kingdom*: R. Eastell, H. Thomas, H. Shaw, H. Donnachie, I. Pavel-Knox, J. Robinson, N. Kola, R. Sarmiento, R. Pawa, N. Savani; *Czech Republic*: I. Kucerova, V. Kuba, V. Vyskocil, S. Kutilek, P. Novosad, J. Slesinger, E. Dokoupilova, J. Doubravsky, J. Gorgol, K. Pavelka; *Estonia*: I. Valter, K. Maasalu, I. Kull; *Greece*: C. Phenekos, G. Lyritis, A. Dimitriadis; *Hungary*: B. Spengler, A. Insperger, T. Balázs, P. Lakatos, K. Takács, I. Szombati, K. Tarján, Z. Valkusz, O. Torma, K. Seregely; *Latvia*: I. Kaze, A. Lejnieks, A. Medne; *Lithuania*: M. Tamulaitiene, D. Velickiene, S. Stonkus; *Malta*: M. Brincat; *Poland*: J. Walecki, M. Bykowska, A. Sidorowicz-Bialynicka, J. Szechinski, M. Korkosz, J. Supronik, M. Koziara, E. Czerwinski, A. Milewicz, S. Jeka, G. Kania, P. Gidzinski, A. Sawicki, W. Tlustochowicz, E. Franek, K. Hoszowski, W. Pluskiewicz, W. Porawska, W. Zgliczynski; *Slovak Republic*: Z. Killinger, P. Masaryk, Z. Kmecova, S. Tomkova, V. Spustova, B. Steno; *Romania*: E. Zbranca, C. Codreanu; *Bulgaria*: V. Hristov, T. Russev, A.-M. Ivanova, R. Velev, M. Mitkov, D. Troev; *Serbia*: S. Brankovic, A. Dimic, N. Pilipovic. **Cardiovascular End-Points Adjudication Committee:** M. Hlatky, N. Goldschlager, D. Herrington, C. Ryan. **Osteonecrosis of the Jaw Adjudication Committee:** C. Migliorati, S. Ruggiero, M. Schubert.

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