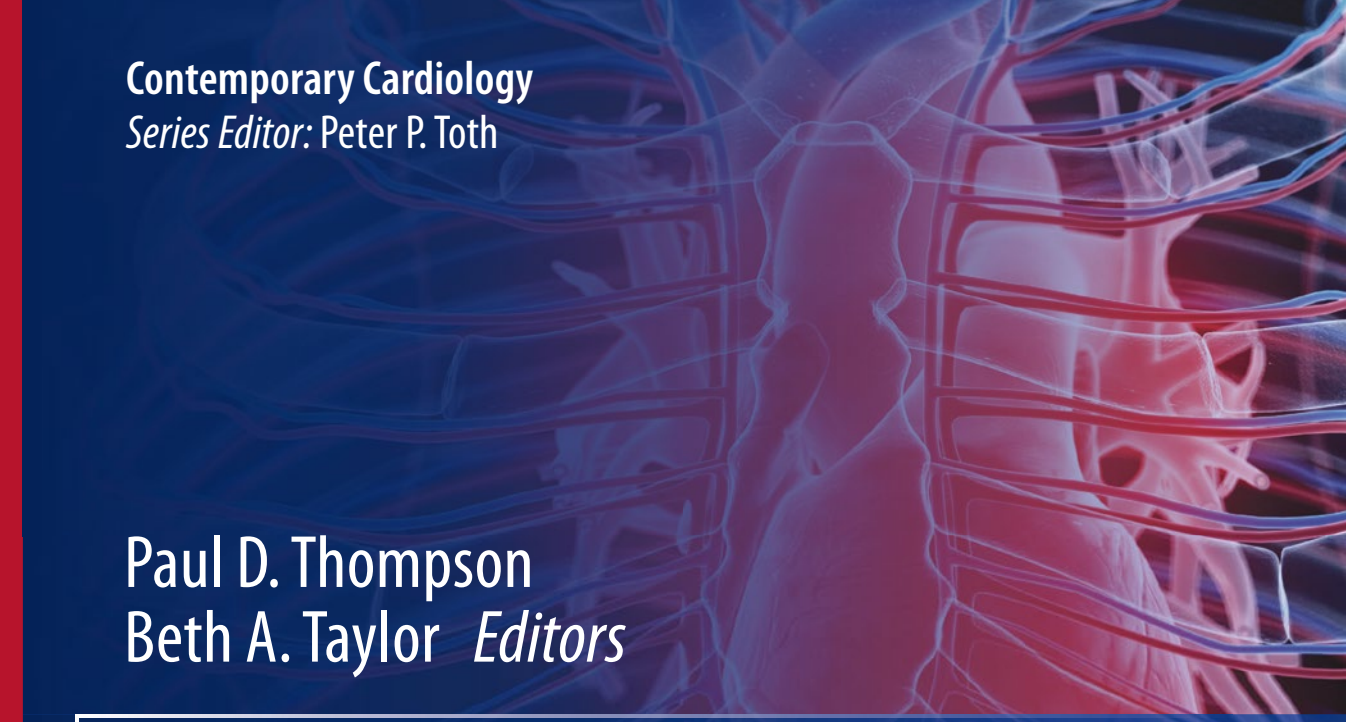

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Statin-Associated Muscle Symptoms

Humana Press

Contemporary Cardiology

Series Editor

Peter P. Toth
Ciccarone Center for the Prevention of Cardiovascular Disease
Johns Hopkins University School of Medicine
Baltimore, MD
USA

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Paul D. Thompson • Beth A. Taylor
Editors

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Editors
Paul D. Thompson
Hartford Hospital
University of Connecticut
Hartford, CT
USA

Beth A. Taylor
Hartford Hospital
University of Connecticut
Hartford, CT
USA

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Preface

Lovastatin was approved by the FDA in July 1987, over 30 years ago. Since then, multiple clinical outcome trials have so consistently demonstrated their ability to reduce cardiovascular disease (CVD) events that the question with statins is often not who should be treated but who should not receive these life-saving drugs. Some authorities have recommended that statins be added to the water supply.

Statins benefit most patients, but they cause side effects that limit effectiveness in some individuals. The most frequently reported side effect is statin-associated muscle symptoms (SAMS), a loosely defined set of symptoms that includes muscle pain, cramping, aching, and stiffness that are attributed to the statin. These are labeled "statin-associated" because there is ongoing debate as to whether or not statins actually cause these symptoms. Part of the debate is due to the fact that the mechanism or mechanisms for SAMS are unknown but could involve altered calcium flux, oxidative stress, mitochondrial function, cell membrane integrity, and apoptotic signaling, since all are implicated in the etiology of SAMS.

We have had a long and interesting journey in studying how statins affect skeletal muscle. Paul distinctly remembers hearing a lecture on lovastatin in the late 1980s which mentioned that lovastatin could increase blood creatine kinase (CK) levels. Paul noted that comment because he had an interest in exercise-related rhabdomyolysis since medical school. At about the same time, Paul was involved in an industry-sponsored trial comparing the effects of lovastatin and fluvastatin on lipid levels. Several of the subjects had demonstrated an increase CK levels soon after exercise. One subject had a CK of 21,400 U/L, 5 days after a weight-lifting session. Paul subsequently embarked on a double-blind, placebo-controlled study which demonstrated that lovastatin-treated subjects experience a 40% higher increase in CK the day after 45 minutes of downhill walking.

Beth, an exercise physiologist, joined Paul in Hartford 10 years ago, and we have continued studies on how statins affect skeletal muscle. These studies have combined our personal interests in exercise and human performance with our interest in lipid metabolism. The mix is even more complex, however, because Paul's interest in lipid metabolism came from his attempts to explain how exercise increases HDL since muscle neither secretes nor directly catabolizes lipoproteins. Many others have been involved in these statin studies. Evan Stein, MD, is a well-known statin researcher who delivered the lecture that mentioned CK levels. Peter Herbert, MD, was an internationally

known lipid expert and Paul's mentor at Brown. Eileen Cullinane, DVM; Linda Bausserman, PhD; and Stan Sady, MD, PhD, were Paul's collaborators at Brown. John Guyton, MD, at Duke obtained the funding for the lovastatin downhill walking study. John was approached by a pharmaceutical company to perform studies and included Paul. Joe Zmuda, PhD, and Richard Zimet, PhD, helped perform that study. Neil Moyna, PhD; Amanda Zaleski, PhD; Gregory Panza, MS; and C. Michael White, PharmD, have been invaluable collaborators at Hartford Hospital.

But, why this book? It has been our experience that patients report SAMS, clinicians treat SAMS, and researchers study SAMS, but often in very disparate settings. We know of no comprehensive textbook that combines the three worlds of patient experience, clinician insight, and investigator knowledge. Indeed, one of our conclusions after reading and editing each chapter was that the study of SAMS requires a collaborative, multidisciplinary approach that has been lacking. The lack of such cohesive clinical and scientific collaborations may contribute to the continuing uncertainty surrounding SAMS, despite it being the most frequently reported side effect of one of the most commonly prescribed classes of drugs.

To create this book, we compiled a list of all the "unsolved problems" surrounding SAMS. We identified the experts in the field who could best present these topics in a way that might elicit new ideas and solutions. To our surprise, almost every author we asked agreed to contribute. We are ever grateful to them for showcasing their collective expertise within these pages.

Several facts are undeniable: CVD is still the leading cause of death in the United States and the world, and statins are an incredibly powerful drug for reducing CV risk. To improve statin use and effectiveness, SAMS need to be better studied, defined, and treated, and this textbook represents what we believe to be a step in that direction.

Hartford, CT, USA
Farmington, CT, USA
Paul D. Thompson, MD

Hartford, CT, USA
Farmington, CT, USA
Storrs, CT, USA
Beth A. Taylor, PhD

Contents

Contributors

Neeltje A. E. Allard, MD, MSc Department of Physiology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

A. Alsolaihim, MSc, MD Department of Medicine, Divisions of Physical Medicine & Neurology, Neuromuscular Disease Clinic, McMaster University Medical Centre, McMaster University, Hamilton, ON, Canada

S. K. Baker, MSc, MD Department of Medicine, Divisions of Physical Medicine & Neurology, Neuromuscular Disease Clinic, Neuromuscular Diseases, McMaster University Medical Centre, Hamilton, ON, Canada

Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA Polish Mother's Memorial Hospital Research Institute, Department of Hypertension, Medical University of Lodz, Lodz, Poland

Marcin Adam Bartlomiejczyk, MSc Polish Mother's Memorial Hospital Research Institute, Department of Hypertension, Medical University of Lodz, Lodz, Poland

Stefano Bellosta, Ph.D. Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

Jean Bergeron, MD Laval University, Quebec City, QC, Canada

Eliot A. Brinton, MD, FAHA, FNLA, FACE Utah Lipid Center, Salt Lake City, UT, USA

Richard D. Childress, MD University of Tennessee Health Sciences Center, Memphis and Veteran's Affairs Medical Center, Memphis, TN, USA

Alberto Corsini, Ph.D Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

IRCCS MultiMedica, Milan, Italy

Flemming Dela, MD, DMSCi Xlab, Department of Biomedicine and Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Department of Geriatrics, Bispebjerg-Frederiksberg University Hospital, Copenhagen, Denmark

Jorge Duconge, PhD University of Puerto Rico, Medical Sciences Campus, San Juan, PR, USA

Marshall B. Elam, PhD, MD University of Tennessee Health Sciences Center, Memphis and Veteran's Affairs Medical Center, Memphis, TN, USA

Nicola Ferri, PhD Department of Pharmaceutical and Pharmacological Sciences, Padova, Italy

David Fitchett, MD University of Toronto, Toronto, ON, Canada

Jacques Genest, MD McGill University, Montreal, QC, Canada

Paul L. Greenhaff, BSc, PhD MRC/ARUK Centre for Musculoskeletal Ageing Research, ARUK Centre for Sport, Exercise and Osteoarthritis, National Institute for Health Research Nottingham Biomedical Research Centre, School of Life Sciences, The Medical School, University of Nottingham, Queen's Medical Centre, Nottingham, UK

Milan Gupta, MD McMaster University, Hamilton, ON, Canada

Robert A. Hegele, MD Schulich School of Medicine, London, ON, Canada

Matthew D. Kostoff, PharmD Clinical Pharmacist of Population Health, University Hospitals, Cleveland, OH, USA

Joanne Mallinson, BSc, PhD MRC/ARUK Centre for Musculoskeletal Ageing Research, ARUK Centre for Sport, Exercise and Osteoarthritis, National Institute for Health Research Nottingham Biomedical Research Centre, School of Life Sciences, The Medical School, University of Nottingham, Queen's Medical Centre, Nottingham, UK

Andrew L. Mammen, M.D., Ph.D Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Expression, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA

G. B. John Mancini, MD University of British Columbia, Vancouver, BC, Canada

Joel C. Marrs, PharmD University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Department of Clinical Pharmacy, Aurora, CO, USA

Patrick M. Moriarty, M.D., FACP, FACC, FNLA, FESC University of Rome, Rome, Italy

The University of Kansas Medical Center, Division of Clinical Pharmacology, Kansas City, KS, USA

Dominic Ng, MD University of Toronto, Toronto, ON, Canada

Gregory A. Panza, Ph.D Hartford Hospital, Division of Cardiology, Hartford, CT, USA

Glen J. Pearson, PharmD University of Alberta, Edmonton, AB, Canada

Peter Penson, PhD School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK

Janet Pope, MD Schulich School of Medicine, London, ON, Canada

Anyelis N. Rosario, BSc University of Puerto Rico, Medical Sciences Campus, San Juan, PR, USA

Robert S. Rosenson, MD Zena and Michael A Wiener Cardiovascular Institute, Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Hospital, New York, NY, USA

Icahn School of Medicine at Mount Sinai, New York, NY, USA

The Lauder Family Cardiovascular Ambulatory Center, New York, NY, USA

Gualberto Ruaño, MD, PhD Laboratory of Personalized Health, Genomas Inc., Hartford, CT, USA

Beth A. Taylor, PhD Division of Cardiology, Hartford Hospital, Hartford, CT, USA

Department of Kinesiology, University of Connecticut, Storrs, CT, USA

University of Connecticut School of Medicine, Farmington, CT, USA

Paul D. Thompson, MD Division of Cardiology, Hartford Hospital, Hartford, CT, USA

University of Connecticut School of Medicine, Farmington, CT, USA

Silvie Timmers, PhD Department of Physiology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

Human and Animal Physiology, Wageningen University & Research, Wageningen, The Netherlands

Peter P. Toth, MD, PhD CGH Medical Center, Sterling, IL, USA

Division of Cardiology, Cicarrone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Amanda L. Zaleski, PhD Division of Cardiology, Hartford Hospital, Hartford, CT, USA

Introduction

1

Beth A. Taylor and Paul D. Thompson

The first commercially available statin, lovastatin, was approved by the Federal Drug Administration in 1987. Over thirty years later, statins are unequivocally considered to be a (if not THE) cornerstone of cardiovascular disease (CVD) prevention and treatment. Why? Statins lower low-density lipoprotein cholesterol by 25–50% depending on the intensity of therapy. Consequently they reduce rates of total and CVD mortality, cardiac and cerebrovascular events, and revascularization by 25–40%, with individual impact varying by baseline LDL-C and magnitude of LDL-C reduction [1]. At a cost of <$300 year/prescription, it is no wonder that these cost-effective and well-tolerated drugs are among the first tools a clinician employs when treating a patient with established CVD or increased CVD risk.

B. A. Taylor (✉)
Division of Cardiology, Hartford Hospital, Hartford, CT, USA

Department of Kinesiology, University of Connecticut, Storrs, CT, USA

University of Connecticut School of Medicine, Farmington, CT, USA
e-mail: Beth.Taylor@uconn.edu

P. D. Thompson
Division of Cardiology, Hartford Hospital, Hartford, CT, USA

University of Connecticut School of Medicine, Farmington, CT, USA
e-mail: Paul.Thompson@hhchealth.org

However, no good deed goes unpunished, and statin drugs are not without side effects. The first cases of lovastatin-associated rhabdomyolysis were reported in cardiac transplant patients in 1988 [2, 3]. Reports of increased CK levels associated with exercise in statin users were reported in 1990 [4]. Despite almost 30 years of such reports and investigations, today we still know remarkably little about statin-associated muscle symptoms (SAMS). The physiological mechanisms of SAMS are not conclusively established and are likely multifaceted. For example, alterations in cellular calcium handling, apoptosis, membrane integrity, and mitochondrial function are among the possible contributors to SAMS [5]. Systemic mechanisms such as low vitamin D levels [6] and exercise-associated exacerbation of muscle damage [7] also appear to have causality to SAMS in some, but not all, individuals.

There are also gaps in our knowledge of how to diagnose and treat SAMS. There are no direct assessments or biomarkers of SAMS besides an increase in CK levels that accompany symptoms in some SAMS patients. Clinicians must rely on patient self-report and drug cessation or drug dechallenge-rechallenge paradigms to confirm the diagnosis, but such approaches cannot avoid the expectation of harm or nocebo effect in some of these patients. Muscle symptoms in SAMS are also nonspecific and variable. Patients report a spectrum of complaints from cramps to pain to weakness that can occur bilaterally or unilaterally,

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in upper/lower/torso muscles or tendons. These symptoms can appear days, months, or even years after initiation of statin therapy. Many patients complain of symptoms bilaterally in large muscle groups that start relatively soon after treatment initiation [8], but many do not. This variability in CK values, symptoms, and symptom onset plus the clinician's dependence on patient self-report of symptoms makes the certain diagnosis of SAMS nearly impossible.

Similarly, treatment strategies such as coenzyme Q10 [9] and vitamin D supplementation may or may not mitigate SAMS. Clinicians are often forced to decrease the statin dose or abandon these drugs altogether. Poor statin adherence is documented to increase the risk of CVD events [10, 11]. Indeed, there is not even consensus that statins cause SAMS in the absence of overt muscle damage as evidenced by increased CK levels [12, 13]. Up to 30–50% of SAMS appear either nonspecific and attributed to non-statin-associated reasons such as aging, disease, or other medications or caused by the nocebo effect, prompted by media reports critical of statins [14], social media, and patient bias [15, 16].

Nevertheless, several facts are undeniable. Approximately 10% of patients report SAMS [17, 18], and SAMS are the primary reason for statin discontinuation. Indeed, 60% of former statin users report having experienced muscle side effects [19]. Patients stopping statins due to intolerance have a markedly increased risk of cardiovascular events with resultant greater healthcare costs [20, 21]. The Centers for Disease Control and Prevention reported that 26% of US adults >40 years of age and 48% of adults >75 years of age report use of a cholesterol-lowering drug and 93% of these use a statin [22]. The 2013 American College of Cardiology and the American Heart Association (ACC-AHA) guidelines for the treatment of cholesterol expanded the number of US adults eligible for statin therapy from 43.2 million (37.5% of US adults) to 56.0 million (48.6%) [23]. Moreover, it has also been estimated that 49.7% of US adults with a high 10-year CVD risk of ≥20% are not receiving statins [24]. Expanding statin use in the United States to the 5.27 million untreated high-risk and 20.29 million untreated moderate-risk adults would prevent 384,000 and 616,000 CVD events, respectively, over 10 years [24]. But effectively expanding statin use to more individuals will require an improved understanding and management strategy of SAMS. Alternative cholesterol-lowering therapies such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and ezetimibe do exist, but their use is limited by expense and effectiveness, respectively, which is also true for agents in development such as bempedoic acid. Thus, an improved understanding of SAMS is critical for directing patients to these alternatives when appropriate.

This textbook seeks to examine the many uncertainties surrounding SAMS, starting with the debate about their very existence and the difficulties in describing and defining their presentation and prevalence. The patient experience, risk factors, and strategies for diagnosis and management are explored. Further chapters present the role of genetics, interventions, and mechanisms in SAMS, as well as interactions between SAMS and physical activity, inherited muscle disease, and inflammation. Each chapter, written by the experts in the field, presents the latest research as well as the controversies surrounding the research and its translation into practice. The aim is to provide in a single source the most updated evidence to inform clinicians and researchers about best patient practice while highlighting essential unanswered questions. Indisputably, the extent to which statins can reduce CVD mortality and morbidity will not be fully realized until we address the nagging issues surrounding SAMS, which remain the most frequently reported yet surprisingly unresolved side effect of these life-saving drugs.

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