Management of Hypertension

Current Practice and the Application of Landmark Trials

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Editors

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Dedication to Edward David Freis

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It is with a great deal of gratitude and pride that I write this dedication to Edward D. Freis, the man, the teacher, the mentor, the giant, my boss. I had the good fortune of knowing Edward D. Freis as a man, as a physician, as a scientist, and as a human being. Ed Freis was a good man, a great scientist, and a great philanthropist. He had a good life and a great career, and he died happy, fulfilled by his achievements, surrounded by his children, and covered by appreciation and respect by his peers.

I first met him in 1981, when I walked into his office looking for a job. I was a research fellow then at the National Institutes of Health, investigating the role of murine macrophages on immunoreactivity, but I had had enough and decided that I wanted to deal with patients. Having heard about Dr. Freis and his work, I called and made an appointment for an interview. It did not take long. After a brief conversation, he said “So, you are interested in clinical research? Ha, and what have you done so far?” When I told him about my experience working with mice, that my group had published 11 papers in 18 months, and that I was more interested in humans, he said “You’ve got the job, when can you start? And by the way, how much money do you make?” After I explained that I was making only $13,000 a year, he said, “We can do better than that: we’ll pay you $18,000.” We had a deal, and I started working with him. Ed Freis was a fair and a generous man. He was fair to his science and supportive
to those who worked for him. By the time I joined his group in June 1981, his landmark work had had a big impact on patient care and the medical community. The treatment of hypertension was widespread, and many other outcome trials were in press or in progress. His work was mostly focused on the treatment of hypertension using diuretic-based regimens. He always held the position that these regimens were safe and effective, but his competitors tried in many different ways to undermine his work. Soon after I joined his group, Dr. Freis attended the American Heart Association’s annual meeting, at which Dr. Bryan Holland presented data from a small study suggesting that diuretics cause arrhythmias and sudden death. This became very controversial and dominated research on hypertension throughout the 1980s and into the 1990s. No wonder Dr. Freis asked me to design a protocol to assess the effect of diuretic-induced hypokalemia on cardiac arrhythmias. The initial study was designed and carried out in patients treated with high-dose diuretics who developed severe hypokalemia. Yet our data indicated no harm from diuretics to our patient population. Even severe hypokalemia had no effect on arrhythmias. After that, we carried out several other studies that repeatedly proved the safety of diuretics. Ed Freis found great satisfaction in these results and continued commenting and writing about them for two decades. Our team and Marvin Moser were the lone defenders of diuretics in the 1980s and part of the 1990s and had several debates and arguments both from the podium and through the literature, but at the end, we were proved correct.

Ed Freis enjoyed life immensely. He prided himself on knowing every good restaurant in town, particularly every good deal (cost-effectiveness). Confidentially, he told me that the best deal was a Greek restaurant called Ambrosia, where one could dine on good food for $15. On numerous occasions, he commented on how much he enjoyed Greek food and in particular my wife’s cooking. Long after he retired, Ed continued coming to the clinic, and in fact, we shared office space for another decade. He authored more than 400 original papers, editorials, book chapters, and reviews. I could write a lot more anecdotal encounters about Ed Freis, but instead I prefer to present a brief outline of his life and commentaries from his students and colleagues following his death.

Edward David Freis was the pioneer researcher who designed and spearheaded the landmark, VA Cooperative studies that
revolutionized the treatment of hypertension. He was born in Chicago on May 13, 1912, and died in Washington on February 1, 2005. He was the youngest of four sons of Roy Freis, a real estate developer, and his wife Rose. Freis grew up in Chicago and graduated from Nicholas Senn High School in 1930. He hoped to become an actor and took time off from college to train at the Pasadena Playhouse. (A sympathetic uncle supported this endeavor, in defiance of his father who vowed to disown his son if he stayed at Hollywood, but later relented.) Freis soon decided that he was not tall enough to succeed in show business and returned to the university, where he got his BS in 1936. Later, he showed great zeal for golf and wanted to become a professional golfer.

Freis had been inspired to pursue a career in medicine after reading Paul De Kruif’s popular books, Microbe Hunters and Hunger Fighters. He received his MD from the College of Physicians and Surgeons at Columbia University in 1940. He completed his internship and residency at Massachusetts Memorial Hospital and the Boston City Hospital, briefly joined the US Army Air Forces (now the US Air Force) and served as assistant chief, and then became chief of the laboratory service at Lincoln Air Force Base in Lincoln, Nebraska, from 1942 to 1944. From 1944 to 1945, he headed the laboratory service for the USAAF Rheumatic Fever Research Program at Gowen Field in Boise, Idaho. After the war, Ed Freis returned to Boston for a cardiology residency at Evans Memorial Hospital, followed by a research fellowship there. Under the supervision of Robert Wilkin, Ed Freis began his clinical research, in hemodynamics and the drug treatment of hypertension, an area that he later revolutionized.

After experimenting with ganglionic blockers, snake venom and hemapheresis, and drugs such as pentaquine, veratrum viride, and hexamethonium, that were effective, but with intolerable side effects, he came across the first diuretic — chlorothiazide — that he studied in a small group of patients and found to be effective and well tolerated. At that time, hypertension was thought to be a normal part of aging, except in severe or in malignant forms.

In 1949, Freis was appointed Assistant Chief of the Medical Service at the Veterans Administration (VA) Hospital in Washington, DC, with a joint appointment as Adjunct Clinical Professor of Medicine at Georgetown University School of
Medicine. He also served as director of Georgetown’s Cardiovascular Research Laboratory (1949–1965) and Chief of the Hypertension Clinic there (1950–1960). In 1954, he became Chief of the VA Medical Service and, in 1959, was named Senior Medical Investigator. During this period, he continued his investigations into the mechanisms and control of hypertension. New antihypertensive drugs were gradually developed, including the ganglion blockers, such as hexamethonium, reserpine, and hydralazine and of course, the first thiazide diuretic, chlorothiazide (in 1956).

At about the same time, the researchers at the VA began a controlled clinical trial to evaluate the growing arsenal of antihypertensive drugs. Controlled clinical trials were something of a novelty at the time, but the VA had done a similar study to evaluate the effectiveness of drugs for treating tuberculosis several years earlier. Although many drugs had been developed during the 1950s for treating hypertension, there was no proof that they provided long-term benefits.

In 1962, Freis formed the VA Cooperative Study Group and designed the landmark VA Cooperative Studies aiming to assess whether treatment of hypertension would help prevent death and cardiovascular complications of hypertension such as stroke, congestive heart failure, kidney damage, and heart attack. The study ran from January 1964 through December 1969, and it was the first randomized, placebo-controlled, double-blind, multi-institutional clinical trial ever done in the United States. The study group included two distinct subgroups of patients: with severe or mild to moderate hypertension. Patients were randomized to either active treatment or placebo. In only 18 months, adverse events in patients with severe hypertension were reduced by more than 90% (21 vs 1 events) and in the mild to moderate groups by more than 50%.

The study results were published in 1969 and 1972, to relatively little fanfare. They attracted more attention the following year, when Ed Freis was honored with a Lasker Award for his leadership of the VA study. Philanthropist and health policy advocate, Mary Lasker, head of the Lasker Foundation, believed that the study revealed a major public health problem that should – and could – be remedied. She asked Elliot Richardson, Secretary of Health, Education, and Welfare, to establish a hypertension education program to alert physicians and the general public about this “silent killer.”
The National High Blood Pressure Education Program was started in 1972 and launched a successful nationwide campaign for hypertension awareness, screening, and treatment. During the next two decades, public awareness of hypertension’s role in heart disease and stroke increased threefold, and the mortality rates from those diseases dropped dramatically. The widespread interest in the United States and around the world in hypertension diagnosis, treatment, and control can be traced back to the work of Ed Freis.

Freis continued to direct cooperative studies on hypertension and to advocate the treatment of the condition, becoming recognized as one of the world’s foremost authorities. In 1979, with science writer Gina Kolata, he wrote The High Blood Pressure Book, a guide for patients and their families, which won the American Heart Association’s Howard Blakeslee award in 1980. Freis broadened his research into various aspects of hypertension treatment, including the role of race in treatment outcomes and the use of medications for elderly patients. He conducted clinical trials on new hypertension drugs, such as the beta-blockers (which slow the heart rate) and angiotensin-converting enzyme (ACE) inhibitors (which block the production of angiotensin II, a hormone that causes blood vessels to narrow) as they were developed. He also participated in many discussions about how and whether to treat mild hypertension.

By the mid-1980s, there were growing concerns about the use of diuretics in hypertension treatment, specifically the danger that they might cause potassium depletion and induce dangerous cardiac arrhythmias and sudden death. Some critics argued that with all the new antihypertensive drugs available there was no need to use “obsolete” drugs like diuretics in any case. He asked me to design and carry out control studies to assess the effect of diuretic-induced hypokalemia on cardiac arrhythmias. Our studies indicated that diuretics were safe and effective and remained the cornerstone of hypertension treatment and control. Freis had long recommended diuretics—which were safe and inexpensive—as the first step in hypertension treatment, alone or in combination with other drugs. Later our position was vindicated by the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) study (1994–2002), which showed that treatment with diuretics controlled blood pressure...
better and was significantly better for preventing cardiovascular disease events, when compared to treatment with ACE inhibitors, calcium channel blockers, or alpha-adrenergic blockers.

Freis retired in 1987 and was named distinguished physician by the VA Medical Center and professor emeritus by Georgetown University School of Medicine. He continued to advise ongoing clinical studies and to publish about hypertension for nearly two decades. At the time of his death on February 1, 2005, he was working on a second hypertension book for a popular audience. That book remained unfinished and given by his daughter to the National Library of Medicine.

Freis mentored a lot of fellows, many of whom later became authorities in the field of hypertension and cardiovascular disease:

**Comments by Edward D. Frohlich:** “Several years ago, while I was Editor-in-Chief of Hypertension, I invited Ed to summarize for the journal some of his more well-known studies emanating from his cardiovascular research laboratory. He reviewed his other work on the hemodynamics of congestive heart failure and myocardial infarction, advancing a new concept of ‘unloading the heart.’ How taken back most investigators were at the thought of administering a ganglion blocking agent in these circumstances to reduce left ventricular preload! He first tried out this concept using a mechanical model of the heart that demonstrated improved cardiac performance when venous return was reduced, using his specially constructed venous reservoir. To my more recent (and personal) thinking and amazement were his studies on blood flow velocity that provided more fundamental support to the earlier clinical reports of Alton Ochsner, who used leg compression by an elastic stocking as a prophylaxis against phlebothrombosis in surgical patients by diverting flow from the more superficial veins to deep veins, thus accelerating deep venous flow. His studies on blood pressure in small arteries, on the velocity of red blood cells and other elements in circulating blood compared with plasma, as well as his work on transcapillary migration of other constituents in the circulation were truly innovative.

No doubt these experiences allowed him to conceive the concept of combination therapy. Each of these various areas of
investigation gave great impetus to those of us who trained with him as well as those who were his research fellows or on our own who later follow through on the foregoing areas as well as with ‘cardiogenic hypertension’, vascular compliance, plasma volume expansion, and aging. It is remarkable, indeed, to see the beginnings of their studies forecasted in Freis’ classic review of the hemodynamics of hypertension in Physiological Reviews in 1960. I still suggest this review as the first reference to be read by fellows in training.”

Comments by Jay Cohn: “What I learned from Ed Freis’ mentorship more than 40 years ago was the virtue of critical, incisive thinking and care in research design. Ed was incredibly disciplined in his life and in his work. His daily routine left little room for spontaneity, from daily naps on his office couch to afternoon golf practice on the field adjacent to the VA Hospital. He tried to teach me a better golf swing, which was his passion. We played rain or shine. One hot day, when I almost collapsed on the 13th tee, he left me lying on the grass with a comment that he would come back for me after he finished the back nine. In scientific discussions he cut to the chase. His desktop was always clear because he dealt immediately and efficiently with all mail and messages. I never learned to discipline my life, which is cluttered with books and papers that I never find time to deal with. But the research integrity and intellectual discipline that Ed demonstrated in our daily encounters have had a profound effect on my career.”

Comments by Edward G. Lakatta: “Ed Freis was my first research mentor. While a medical student at Georgetown University, I had not previously been exposed to research and wished to find out what it was like. Ed’s genuine zeal for research rubbed off on me! We spent substantial periods of time planning experiments, interpreting results, and, subsequently, writing up the findings. He instilled in me the confidence needed to deliver my first paper describing our results at an American Heart Association Meeting, a rare experience for a medical student. Because of my interaction, I developed a passion for research that has never dwindled. Following my training in internal medicine, I spent 2 years at NIH studying cardiac muscle changes with aging. Later, when I was a fellow in cardiology, Ed made another substantial impact on my career. He and others at the Washington VA Hospital had made remarkable contributions to hemodynamics research, and I was
poised to commit to this area of research as well. Ed advised me, however, that the door toward understanding the mysteries of the cardiovascular system was not via hemodynamics but in heart cell research, (ie, the type of stuff I had explored at NIH). I heeded this advice and have enjoyed a challenging 30-year career doing so, and following in his footsteps.”

Many other fellows credit their work and interests to Ed Freis, to name a few:

**Robert Tarazi**, fellow at the Cleveland Clinic, would credit Ed Freis’ concept of cardiogenic hypertension for his personal interests in that area.

**John Rose**, who became the Chairman of Physiology at Georgetown and later Dean of the Medical School, in reflecting about Ed Freis, said that he became a research fellow after his internship in 1951 and “I was a close personal friend ever since. He was a remarkable guy, a great teacher: gentle, kind, and prodding. But, in the experimental laboratory of the early 1950s, he was also compulsive, having all of the qualities of a true scientist, intensity and stress when things were not going well!” As a former Dean of the School of Medicine, Rose was justly proud to say that Ed donated his Lasker Awards to the university for display.

**Dr. Larry Lillienfield**, another research fellow of Freis, succeeded John Rose as Chairman of Physiology and commented, “Ed was a wonderful guy who made a tremendous impact on the fundamentals of cardiovascular physiology as well as the more widely known contributions in the area of clinical hypertension.”

**Barry Materson** wrote the following: “I owe him big and I remember telling him that every time that whenever I spoke with him. He was a great mentor even though I never worked directly for him. I enjoyed playing golf with him, and he not only tolerated playing with me but also gave me some lessons in the process. Ed Freis was never swayed by the dogma of the moment unless it was thoroughly back by valid data. He demanded databased opinions long before evidence-based medicine was popularized.”

**Ed Frohlich** writes: Another successor to Freis’ work was Vasilios Papademetriou at the VA Hospital in Washington. At Ed’s funeral, Vasilios commented in his warm and thoughtful
eulogy that “Ed Freis was a good man, someone who served science religiously but also someone who enjoyed life tremendously.

He was a great man, and had a good life, a brilliant career, and passed away quietly.”

Ed Freis had an impact in medicine like only few others. His work on hypertension changed the course of history and saved untold hundreds of thousands of lives. His name and his work will remain imprinted in the literature forever.

“He was a good man, a great scientist, and an amazing mentor. He was one of the giants, he was my boss.”

Edward D. Freis (1912–2015)
It is with great pleasure and excitement that we publish this book, entitled *Management of Hypertension: Current Practice and the Application of Landmark Trials*. Hypertension is indeed a major public health problem worldwide and the most widely recognized modifiable risk factor for cardiovascular disease, with an estimated overall prevalence in adults, aged 25 and over, around 40% in 2008. As such, it is a subject that gathers a special interest among physician-scientists involved in cardiovascular research. With the completion of this project, we aim to offer to young physicians and other scientists engaged in the clinical cardiovascular field a book that reviews the milestone hypertension trials that changed the false belief that was dominating at the dawn of the twentieth century and which supported that blood pressure was essential for the perfusion of vital organs and, therefore, it should not be treated. The studies of Irvine Page, who first observed that despite lowering blood pressure using colloidal sulfur injections, kidney function was well maintained and the first who described the famous mosaic theory of hypertension, as well as the first randomized controlled trials conducted by the farsighted physician, Edward D. Freis, were pivotal in changing the “medieval” understanding of this devastating condition, once and for all.

This book is organized into five major parts. The first part is an introduction to medical research. Its objective is to help scientists and hypertension specialists understand the importance of applying evidence-based medicine in clinical practice, and become familiar with the basic concepts in biostatistics, which will assist them in interpreting the results of scientific papers – it helps them, in particular, to recognize the strengths and weaknesses of a published work. We believe it is of critical importance for a scientist involved in the cardiovascular field to understand deeply the process of analyzing and interpreting medical data.

The second part that comprises 11 chapters review some of the major landmark studies which answered some of the most important questions that altered the course of the investigation and treatment of high blood pressure and influenced the lives of many hypertensives around the world: Is arterial hypertension linked to increased cardiovascular risk? Should we treat higher levels of diastolic blood pressure in adults? Should we treat isolated systolic hypertension in older persons? What is the best way to treat high blood pressure? The VA Cooperative studies – the first randomized controlled trials anywhere in the world – the DASH, the SHEP, the AASK, the ASCOT, the ACCOMPLISH, the MRC, the HDFP, the HOT, the ACCORD, the SPRINT,
and the HOPE3 are only some of the major hypertension trials discussed in this part. How did they influence the management of hypertension? This part also reviews the recently updated 2017 ACC/AHA Guidelines for the management of hypertension and tries to examine the advantages and disadvantages of clinical trials.

In the third part of this book, there is only one chapter that reviews the methods of blood pressure assessment used in milestone hypertension trials.

The fourth part is dedicated to three of the most important and pioneer researchers in hypertension research: Dr. Irvine Page, Dr. Edward D. Freis, and the legendary Stevo Julius who is still actively involved in hypertension research. We cordially want to thank Dr. Brent Egan who willingly accepted to review his major scientific contributions in the field of hypertension.

The last part of this book takes a look into the future of cardiovascular medicine with the advent of microfluidics. How these could be applied in hypertension research is a subject discussed thoroughly in the last chapter of this part.

For the completion of this project, we did invite as authors hypertension experts who are widely recognized as global leaders in the field of cardiovascular research. We deeply appreciate their time and work to expertly and concisely review the milestone hypertension trials discussed in this book. Each chapter merits multiple reads and can be read as a unique manuscript, and therefore, any overlapping in the mention of some of the landmark studies was inevitable. These chapters can act as a starting point for anyone seeking an up-to-date and scientifically accurate review regarding the hypertension landmark clinical trials. Their outstanding work has given this book the opportunity to succeed as an educational resource for the scientific community and to enhance the clinical skills of practicing physicians. Most importantly, we would also like to give special thanks to Professor Costas Tsioufis, the President of the European Society of Hypertension and the President of the Hellenic Society of Cardiology, our friend and collaborator, who supported our work by endorsing our book as an ESH endorsed book and contributed a valuable chapter to this book.

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Vasilios Papademetriou
Emmanuel A. Andreadis
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Dr. Andreadis and I, on behalf of all contributors, wholeheartedly want to thank Dr. Charalampia (Chara) Geladari, for all she has done to make this book possible. Chara has been the heart and soul of this publication, took care of every little detail, and put bright colors on every page of this book. We all thank you Chara!

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Last but not least, I want to thank my family for putting up with me, despite my frequent travels and long leave of absence.

I thank you all.

Vasilios Papademetriou, MD, PhD

I would like to thank my associates, Professor Vasilios Papademetriou and Dr. Charalampia (Chara) Geladari for the accomplishment of this great book. Professor Papademetriou and I are especially grateful to Chara, my dedicated colleague, for her enthusiasm, creativity, and commitment and for her exhaustive and thorough work. This book could not have been written without her generous assistance.

I would like to express my immense gratitude to my wife for her help and, of course, to my daughter for her encouragement in my clinical and research activities. To all of them, I extend my deep appreciation.

Emmanuel A. Andreadis, MD, PhD.

I would like to express my deepest gratitude to my mentor Emmanuel A. Andreadis for believing in me and for being my inspiration to pursue my goals with hard work and dedication. I cordially thank you, Dr. Andreadis, for your sincere support, commitment, time, and mentorship! You have made an impact on my life. To me, you are absolutely family!

I would also like to thank Professor Vasilios Papademetriou for this great opportunity, to be one of the editors of this book, and for his support and trust. Dr. Papademetriou, it is truly an honor to work with you!

My warmest thanks to my family for their unconditional support, encouragement, and love!

Charalampia Geladari, MD.
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Part I

Introduction to Medical Research
The Importance of Applying Evidence-Based Medicine in Clinical Practice

Thomas Karagiannis

What Is Evidence-Based Medicine?

The first scientific origins of evidence-based medicine (EBM) can be traced back to mid-nineteenth century in the works of John Snow and Pierre Charles Alexandre Louis [1], or even earlier in James Lind’s study on scurvy [2]. Despite these innovative attempts, clinical practice in medicine was still largely based on expert opinion, driven by physiological rationale and individual clinician’s expertise. It was not until mid-twentieth century that the medical community began to realize that reliance on uncontrolled clinical experience and pathophysiological reasoning alone, was flawed [3]. In fact, in 1962 the Food and Drug Administration passed the Kefauver-Harris Amendment in the United States, which required evidence from rigorous clinical trials in order to determine drug efficacy [4]. Later, in the 1970s and 1980s, the seminal works of Archie Cochrane [5], David Eddy [6] and David Sackett [7] further highlighted the need for strengthening the empirical practice of medicine and established the key concepts behind evidence-based practice.

The first published use of the term “evidence-based” in medical literature appeared in a series of articles by D. Eddy in 1990 [8]. These papers discussed the limitations of expert opinion in medical decision making, but focused mainly on the development of clinical guidelines, arguing that these should be based on substantial evidence, rather than subjective judgment or consensus. In 1991, G.H. Guyatt introduced the term “evidence-based medicine”, which differed from the definition proposed by D. Eddy, as it had a more clinical orientation, promoting the careful assessment of existing research evidence by physicians and its application in their daily decisions about individual patients [9]. A more comprehensive article, published a year later by the EBM Working Group, presented EBM as a novel paradigm in the teaching and practice of medicine [10], while the User’s Guides to the Medical Literature series in JAMA brought the underlying concepts of EBM to the attention of a wider medical community [11]. Subsequently, the influence of EBM has been constantly growing worldwide, resulting in its recognition as one of the most important medical milestones since 1840 [12].

The Principles of Evidence-Based Medicine

In its most commonly cited definition, EBM is described as “the conscientious, explicit, and
The judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research” [13]. Later, this definition was refined, emphasizing the importance of patients’ values and preferences in optimal clinical decision making. As a result, EBM can more accurately be described as the “integration of best research evidence with clinical expertise and patient values” [14], as depicted in Fig. 1.1. A variation of this characterization has also incorporated the clinical state and circumstances within the context of clinical expertise [15], while in a broader definition, that of evidence-based practice, health care resources are also considered an important parameter for optimal decision making [16]. Regardless of the exact definition used, the principles of EBM emphasize that all medical decisions about a therapeutic or diagnostic procedure should be based on high quality, up-to-date research evidence, acknowledge the importance of clinical expertise and intuition and highlight that patient value and preference judgements are implicit in every clinical decision.

Best Research Evidence

Research evidence originates from various types of studies, including laboratory observations, pathophysiologic studies, case reports, observational studies, or more advanced applied clinical research from randomized controlled trials (RCTs). EBM acknowledges that not all research is created equal and that some study designs are more suitable than others in answering specific research questions [1]. Therefore, EBM, from its early inception, has suggested a hierarchy for ranking the quality of evidence [17]. Figure 1.2 illustrates such a hierarchy framework of evidence. The pyramid shape is used to represent the decrease in risk of bias (or increase in quality) associated with each study type as one goes up the pyramid.

In this hierarchy, RCTs are placed at the highest level of the pyramid, thus represent the most reliable evidence for determining the effectiveness of medical interventions, as opposed to observational studies or other study designs. Notably, since the first documented report of an RCT in 1948 (streptomycin treatment for pulmonary tuberculosis [18]), the RCT has been considered as the most scientifically rigorous method for hypothesis testing [19]. In a typical RCT, participants are randomly allocated to one or another intervention and are followed for a specific period. At the end of the study, any differences observed in predefined outcomes are attributed solely to the trial intervention [19].
However, it is now recognized that evidence from RCTs is not necessarily always of high quality and that not all research questions can be answered through an RCT [1]. For example, the diagnostic accuracy of a medical test can be answered from a well-conducted cross-sectional study, while an observational study is required for a question about prognosis [13]. On this account, a revised form of the traditional evidence pyramid has been proposed, in which the straight lines separating study types have been converted to wavy lines, suggesting that there is overlap in study quality among different designs [20]. For instance, it is possible that for a specific research question observational studies provide more reliable information than RCTs. Furthermore, quality of evidence does not depend solely on study type, but on other parameters as well, such as bias in study implementation, imprecision, inconsistency and indirectness. As a result, a more sophisticated approach to rating evidence quality has been developed, termed the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system [21]. In the GRADE framework, non-RCTs begin as low-quality evidence, but can be rated up based on the parameters mentioned above, as opposed to RCTs, that start at high level and can be rated down.

Systematic reviews and meta-analyses are an additional important tool of EBM [22]. A systematic review provides a summary of all primary studies about a specific clinical question, using predefined methods for identifying, critically appraising and synthesizing all available research evidence. Due to their explicit methodology and cumulative data synthesis, systematic reviews are considered to provide more reliable and accurate conclusions compared to individual studies [22].

**Clinical Expertise**

The practice of EBM dictates that research evidence alone is inadequate for optimal decision making if the information is not efficiently combined with clinical expertise. Clinical expertise includes the general basic skills and proficiency acquired through clinical practice, as well as the experience of the individual practitioner [23]. Clinical expertise can be reflected in many ways, including obtaining the right diagnosis, determining relevant treatment options and placing research evidence within the context of the individual patient’s clinical state and circumstances [23, 24].

Obtaining a history and conducting a physical examination are essential skills for getting the right diagnosis, that come only from thorough background training and clinical experience [24]. In addition, many diagnostic tests may differ in their accuracy depending on the skill of the practitioner [10]. In a similar manner, the effectiveness and complications associated with therapeutic interventions, particularly surgical interventions, can also depend on individual clinician’s experience and skills [10]. Finally, after obtaining the best relevant research evidence, the clinician, using sound clinical judgement, must determine whether the external evidence can be applied to the individual patient. In doing so, the clinician must consider all relevant comorbidities that may influence the treatment effect, in addition to research-related factors, such as whether the available studies have measured all important outcomes, included relevant comparators and have a reasonable follow up period [24, 25]. Additional features of clinical expertise are related to the ability to provide patients with the information they need in a manner that facilitates informed decision making and developing values such as integrity, compassion, respect and sustained professional curiosity [15, 26].

A concise definition summarizing all the essential characteristics that constitute clinical expertise, has been given by W.S. Richardson: “Clinical expertise includes the deliberate practice of communication skills, clinical skills, and decision skills, as well as the experiential learning that comes through the care of sick persons, with the development of clinical judgment” [26].
Patient Values and Preferences

Clinical expertise and knowing the best research evidence are necessary, but insufficient for delivering the highest quality of care. The third key principle of EBM advocates that clinical decisions and recommendations must attend to the values and preferences of the informed patient. This patient centered approach means that it is not the clinician who should exclusively decide what will happen to the patient, but it is also the patient’s right to participate in decision making about their treatment options or diagnostic procedures [27].

Values and preferences refer to patient characteristics that can variably affect decision making during the clinical encounter. These may include experience of former and current illnesses or other relevant life experiences, health habits, goals and expectations, social or family support, and personal beliefs about medical interventions [26]. Depending on these factors, patients may have either no views or unchangeable views on how to proceed with their treatment or diagnostic options. Of note, research has shown that considerable variation exists between physicians’ and patients’ preferences when it comes to weighting the benefits and drawbacks of therapeutic options [28]. Moreover, patients’ actions may differ not only from their clinician’s advice, but also from the preferences and views they expressed during the clinical consultation [15]. Thus, in addition to exploring patients’ perceptions and values, a clinician should ideally be able to understand the procedures individuals use to consider their treatment options, in order to assess whether patients are likely to adhere to their prescriptions and therapeutic recommendations [29, 30].

From an ethical point of view, respecting patients’ preferences should be justified on moral grounds alone [31]. Patient centered care has a theoretical foundation in the principle of patient autonomy, a belief that originates from the patients’ rights movement in the 1960s [32]. Since then, several medical associations, institutions and health planners have endorsed and incorporated patient centered care in their guidelines, recommendations and policies. In fact, the National Health Service Constitution in the United Kingdom advocates patient participation in decision making [33], while in the United States, the Institute of Medicine, in its “Quality Chasm” report, has designated evidence-based patient centered care as one of six key elements of high quality care [34].

Applying Evidence-Based Medicine in Clinical Practice

The practice of EBM involves a multi-stage process [35]. First, the clinical problem must be translated into an answerable question. Subsequently, one needs to retrieve the best evidence that answers this question and critically appraise the findings with respect to their validity and usefulness. The fourth step involves implementing the results of the appraisal into clinical practice, while the final step is related to evaluating the effectiveness and efficiency in executing previous steps and seeking ways to improve them [35].

It has been suggested that clinicians can incorporate this five-step process into their practices in three different ways [35]. First, in the “doing” mode, at least the four first steps are followed before a medical decision is made. In the “using” mode, step 3 is skipped by restricting the search to evidence that has already undergone critical appraisal, such as databases of guidelines or pre-appraised information. Finally, in the “replicating” mode, decisions are based on respected leaders’ opinion, thus both steps 2 and 3 are omitted. Ideally, the “doing” mode should be followed in most cases, however depending on the specific clinical problem they encounter, physicians can move back and forth between the three modes [35].

Formulating an Answerable Question

The practice of EBM should begin with a well formulated clinical question. Several times a day, physicians are asked to come up with answers to various clinical problems in order to make
medical decisions. Questions that arise for most clinical situations are typically divided into two broad categories [36]:

- **Quantitative questions**, which aim to discover cause and effect relationships by comparing two or more individuals or groups based on differing outcomes associated with exposures or interventions.
- **Qualitative questions**, which aim to discover meaning or gain an understanding of a phenomena.

A more detailed categorization of clinical questions, based on their type and the respective study design that is most appropriate to provide answers, is presented in Table 1.1.

The questions that arise may be unstructured and complex at first, but it is important that they are translated in a clear form before proceeding to literature search. A good clinical question should be directly focused on the problem at hand and structured in a form that can be answered by searching the medical literature [37]. Without a well-formulated question, it can be impractical and very time consuming to search for and identify relevant evidence. Practitioners of EBM often use a specialized framework, called PICO, to form more focused and relevant questions [38]. PICO stands for **Patient** (or condition), **Intervention** (or diagnostic test or exposure), **Comparison**, and **Outcome** (or diagnosis/development/prevention of a condition). The PICO format can be expanded to PICOT, adding information about the **Type** of question being asked (for example therapy, diagnosis, prognosis) or the most appropriate study design for that particular question [39]. Notably, research has shown that the PICO format can help clinicians formulate more precise questions and develop more detailed search strategies [40, 41].

### Identifying the Best Evidence

After having formulated an answerable and clinically relevant question, the next step is to track down the best available research evidence. In years past, searching for answers in the medical literature was a very daunting process, but nowadays the development of internet and large electronic databases has made searching and retrieval of information much easier. To further facilitate the identification of high quality evidence for a particular clinical problem, the EBM Working Group, in its guidance series, originally proposed a 4S model for ranking the quality and validity of various sources of evidence [24]. This 4S model has now been refined to a 6S pyramid that represents a hierarchy of six literature sources [42]. Similarly to the hierarchy based on study design [25], the quality of evidence increases as one goes up the pyramid. As illustrated in Fig. 1.3, the 6S pyramid begins with original primary studies and builds up to synopses of studies, syntheses (systematic reviews), synopses of syntheses, evidence summaries and systems [42].

When using the 6S model to retrieve research evidence, one should begin their search at the highest layer. Ideally this would be the “systems” layer, placed at the peak of the pyramid. “Systems” refer to computerized decision support systems, in which individual patient’s characteristics are automatically linked (through

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### Table 1.1 Types of clinical questions and appropriate study designs

<table>
<thead>
<tr>
<th>Type of question</th>
<th>Interpretation</th>
<th>Type of study</th>
</tr>
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<tbody>
<tr>
<td>Treatment</td>
<td>How do we select among different treatments?</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>How do we identify whether a person has a specific condition?</td>
<td>Randomized controlled trial or cross-sectional study</td>
</tr>
<tr>
<td>Prognosis</td>
<td>What is a patient’s likely clinical course over time?</td>
<td>Cohort study</td>
</tr>
<tr>
<td>Etiology/prevention</td>
<td>How do we identify/prevent the causes of a specific condition?</td>
<td>Cohort study</td>
</tr>
<tr>
<td>Experiences</td>
<td>How does it feel to have a specific condition?</td>
<td>Qualitative study</td>
</tr>
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an electronic health record) to all important research evidence that are relevant to a specific clinical problem [43]. Subsequently, all key information is concisely summarized for clinicians in the form of patient-specific assessments or recommendations. However, to date few such systems are available, therefore one would need to look for “summaries” as the next best source. These “summaries” include pre-appraised resources of evidence that are regularly updated and integrate evidence-based information about specific clinical problems [42]. Such sources include DynaMed [44], UpToDate [45], BMJ Clinical Evidence [46] and BMJ Best Practice [47]. An additional type of pre-appraised summaries are clinical practice guidelines, provided they are based on comprehensive search and appraisal of the literature and report levels of evidence for each recommendation.

If a clinical question cannot be answered through a “summary”, then a synopsis of a synthesis (systematic review) is the next step. A good synopsis summarizes the main methods and findings of a high quality systematic review, providing sufficient information to support clinical action [42]. Such synopses are available in the Database of Abstracts of Reviews of Effects (DARE) [48] and in specific journals, including ACP Journal Club [49] and Evidence-Based Medicine [50]. Notably, other than systematic review summaries, these evidence-based abstraction journals also provide summaries of individual primary studies.

If more detail is needed or no synopsis is available, one should look for original systematic reviews or primary studies. These can be identified through search of electronic databases, such as PubMed, EMBASE and the Cochrane Library, by using relevant keywords (based on the PICO format of the clinical question) and specific study type search filters [51]. Finally, search engines like TRIP [52] or Epistemonikos [53] sort evidence across a broad range of various sources, including guidelines, structured summaries, systematic reviews and primary studies.

Fig. 1.3 The 6S pyramid of evidence sources

Critically Appraising the Evidence

Not all published research is good or even transferable to a particular patient. Therefore, the evidence retrieved from the literature search during step 2 must be critically appraised in terms of its quality (internal validity) and generalizability or applicability (external validity) [54]. Assessment of external validity of research findings is an issue regardless of the source of evidence, as it is related to whether the patient of interest differs significantly with the reference population, in terms of clinical or demographic characteristics, such as comorbidity, age, stage of disease, overall health status or concomitant medications. With regards to internal validity, it is reasonable to assume that evidence from most pre-appraised literature sources has been adequately peer-reviewed beforehand; however, this is not the case with primary research, such as individual studies, systematic reviews or even some guidelines. On this account, expert committees have issued formal guidance for optimal reporting for different types of studies. These are available at the EQUATOR website [55] and include CONSORT [56], STROBE [57], PRISMA [58] and RIGHT [59] statements for RCTs, observational studies, systematic reviews and clinical practice guidelines, respectively. In addition, useful tools for critical appraisal covering a wide range of research designs have been developed by the Critical Appraisal Skills Programme (CASP) and are freely available online [60].
Implementing the Results in Clinical Practice

The fourth step is perhaps the most complex, as it involves adjusting the evidence findings to the unique clinical circumstances, personal values and preferences of an individual patient. Under this premise, all relevant key evidence should be fully discussed during the clinical consultation, allowing for a therapeutic alliance to be formed between the patient and the clinician [37]. In particular, information should be tailored to patients’ needs in order to permit meaningful deliberation and ideally facilitate shared decision making [31]. The shared decision making model has been seen as a mechanism of decreasing the informational and power asymmetry between patient and physician, by increasing patients’ knowledge, enhancing their sense of autonomy and engaging them in making decisions, insofar as they wish to participate [61]. Shared decision making is increasingly advocated as an ideal model for most medical encounters and several countries have adopted policies that support its implementation within their healthcare systems [62]. It should be noted however, that shared decision making does not mean merely presenting the patient with a series of decision options alongside their respective advantages and drawbacks. Instead, real shared decision making involves introducing research evidence in a way that informs a dialogue about what matters to the patient, what is the best course of action and how this may affect the patient’s well-being [63].

To facilitate this patient centered approach, a variety of tools for use during the clinical consultation have been developed for several medical conditions. According to a Cochrane systematic review, these decisions aids are “interventions that support patients by making their decisions explicit, providing information about options and associated benefits/harms, and helping clarify congruence between decisions and personal values” [64]. Two distinct types of decision aids have been described, patient decision aids (PtDAs) and conversation aids. Both types include a concise description of current research evidence about a medical condition and relevant treatment (or diagnostic) options, in a manner that can be easily understandable by patients [65]. However, while PtDAs aim is to improve patient knowledge and encourage patient involvement in decision making, conversation aids take this process one step further, by directly supporting and improving the quality of conversations that patients and clinicians have when making decisions together [66].

Evaluating the Overall Process

The fifth and final step involves evaluation our overall approach at frequent intervals in order to decide whether we need to improve any of the four steps. During this process, we need to ask whether we have formulated answerable questions, effectively identified and critically appraised the literature and integrated best available evidence with our clinical expertise and patient’s values in the decision making [37]. In addition, it is also important to assess whether our overall approach has had a favorable effect on patient important outcomes. Interestingly, self-evaluation tools in practicing EBM are available online [67], while, according to a Cochrane systematic review, external audit and feedback on the practice of healthcare professionals can improve their performance [68].

The Importance of Evidence-Based Medicine

Despite its widespread recognition, EBM has also received criticism both by clinicians and researchers. However, as explained below, most of these criticisms are misperceptions, either of the definition of EBM or the way it should be practiced. Once cleared up, these misinterpretations highlight the benefits and importance of EBM.
Evidence-Based Medicine Is Superior to Experience-Based Medicine

Given that clinical practice has long been dominated by expert opinion and many guideline committees have used, and probably still use, expert consensus to make recommendations, one could argue that physiological reasoning and expert opinion should be the main drivers in clinical decision making. It has also been claimed that EBM does not represent a scientific approach to medicine and that reliance research evidence when making medical decisions, is problematic [69].

However, there are many examples where EBM, through the use of either RCTs or systematic reviews, has rightfully questioned unsubstantiated therapeutic claims of interventions that were later proven to be ineffective or even harmful [24]. It was only after the completion of RCTs, that administration of growth hormone in critically ill patients [70], ibopamine [71] and epoprostonol [72] in heart failure, and beta-carotene in patients with prior myocardial infarction [73] were associated with an increased mortality rate. Similarly, an RCT was necessary to establish the favorable effects of beta-blockers in reducing mortality in congestive heart failure, despite long-held beliefs that their negative inotropic action would be detrimental to these patients [74]. Well-conducted systematic reviews have equally contributed in improving the standards of healthcare [1]. Such examples include incorporating use of short course of oral steroids for community-acquired pneumonia [75] and establishing standards of care for early breast cancer [76]. Moreover, uptake of guidelines can have a major beneficial community effect, provided their development is supported by robust research evidence, as demonstrated by a decrease in asthma-related morbidity and mortality [77] and reductions in thromboembolic complications [78]. Of note, the Academy of Medical Royal Colleges in the United Kingdom has recently launched a booklet titled “Evidence based medicine matters”, which contains 15 examples where EBM has benefited clinical practice in various medical specialties [79].

Evidence-Based Medicine Encourages the Development of Clinical Skills and Expertise

A common criticism of EBM is that it represents a “cookbook” in the sense that it regards clinical expertise mainly as a matter of collecting, analyzing and summarizing research done by others [80]. It has also been suggested that EBM, by encouraging blind adherence to guidelines, has shifted clinical decision making from the consultation room to the “professional association” [27]. Nevertheless, since the inception of EBM, its proponents have highlighted that external clinical evidence should not replace, but complement a physician’s clinical intuition and judgement during the decision making process [13]. In fact, the original guidance series issued by the EBM Working Group underscore that a good understanding of the pathophysiological background of the disease in addition to clinical skills, such as careful history taking and physical examination, play a crucial part in the implementation of EBM [10]. Moreover, it is highlighted that teachers of EBM should be exceptional clinicians with a talent of precise observation, a gift for intuitive diagnosis and excellent judgment in making difficult management decisions [10]. Therefore, rather than diminishing the role of expertise and judicious clinical judgment, appropriate application of EBM values experiential thinking and encourages physicians to continuously improve or acquire new clinical skills. Even though some practitioners of EBM may also do research, it is important to remember that its practice is a method for providing care for patients and not a method for performing research [35].

Patients Are at the Core of Evidence-Based Medicine

Evidence-based medicine has also been accused that it disregards patients’ unique knowledge and experience and ignores their needs and preferences [81]. Sweeney et al. suggest that EBM represents a doctor centered, rather than a