Tulio Pinho Navarro · Alan Dardik
Daniela Junqueira · Ligia Cisneros *Editors*

Vascular Diseases for the Non-Specialist

An Evidence-Based Guide

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ISBN 978-3-319-46057-4 ISBN 978-3-319-46059-8 (eBook)
DOI 10.1007/978-3-319-46059-8

Library of Congress Control Number: 2016960550

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

With the surfeit of vascular surgical textbooks, one might wonder why another book is necessary. The editors have taken a different route from most vascular texts and organized a compendium of chapters designed for the nonvascular individual, which would include medical students and allied professionals such as physician assistants, nurse practitioners, and even scientists in the biological world. I would argue with this focus by the editors in that this text also has exceptional value for the trainee and practitioner of vascular medicine and surgery. This is not a text for how to do particular procedures but rather how to think about the enormous variety of pathologies encountered by those dealing with vascular disease. The chapters are well written and have been edited to provide a smooth transition as one progresses through the various systems. The basic sciences are not neglected. In fact, commentaries dealing with biology, pathology, and pharmacology are matched by sections dealing with statistics, epidemiology, and gathering of information. This is truly an unusual text assembled under the guidance of two experienced vascular surgeons. This book is readable, practical, and will not be relegated to obsolescence. This text is an excellent source of practical information for the novice as well as the expert healthcare provider.

Herbert Dardik
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Preface

Over the last several decades, improved healthcare systems coupled with improvements in public health works such as sanitation have led to major epidemiological shifts and alterations of prevalent trends in nosology. One of these changes is the general improvement in health allowing people to live longer and better. The price for this, however, is the aging population that is burdened with nontransmissible chronic disease. Atherosclerosis is now the leading cause of death worldwide, responsible for one-third of deaths; as such, vascular diseases are now widely prevalent and are currently a major public health issue. Vascular diseases such as aneurysms, peripheral arterial disease, the diabetic foot, venous thromboembolism, cerebrovascular disease, aortic dissection, and acute limb ischemia are now much more common, especially in emergency rooms.

However, many healthcare practitioners have little or no knowledge about the modern diagnosis and therapy that are appropriate for these common vascular diseases. Interestingly, each of these vascular diseases has its own risk factors, demographics, natural history, and treatment; even peripheral artery and coronary artery disease are quite distinct. Simply using a non-evidence-based approach could increase morbidity and costs of treatment, and even lead to mortality.

The idea of this book was born after we realized that most of our undergraduate students and nonvascular expert healthcare professional colleagues did not have an objective evidence-based guide for their education and daily practice. Most of the vascular textbooks available to them are typically intended for experts and not for general practitioners.

The aim of this book is to provide nonspecialist healthcare practitioners with current, focused, objective, and evidence-based information on the most common vascular diseases encountered in daily clinical practice. For each disease, the concept, epidemiology, natural history, diagnosis, and treatment are described, followed by essential advice on what the nonspecialist can do for the patient and when to refer the patient to a specialist.

Belo Horizonte, Minas Gerais, Brazil — Tulio Pinho Navarro
New Haven, CT — Alan Dardik

Acknowledgements

A publication of this magnitude is accomplished only by the combined efforts of many people. We would like to acknowledge the persistence and dedication of all involved in this project, especially the chapter's authors who contributed their expertise and the reviewers that took part in the process of improvement of quality, coherence, and content of the chapters.

A very special thanks to Raquel Ferreira Nogueira, who ignited the idea to provide a book for nonexperts; once as an undergraduate student, she only had access to textbooks intended for experts. She also gathered our group of undergraduate students as contributors and started all the process that ended in this book.

Another special thanks to Patric Oliveira Gonçalves for the invaluable support, helping the authors in their quests. His work in this project was *sine qua non* for finishing the book in time, organizing all chapters and files with unique competence.

We would like to express our gratefulness to Mariza Cristina Torres Talim, librarian of the Faculty of Medicine's Library of Federal University of Minas Gerais, for the willingness in helping the authors with the End Note software.

We thank the editorial staff of Springer, especially Gabriel Pires, from Springer Brazil, who gently and patiently helped us during all the process of this book.

We hereby acknowledge our families for encouraging and supporting our mission and for the patience and understanding that editing a book is not a simple task.

The editors

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How to Make Decisions in Healthcare?

1

Daniela R. Junqueira

Abstract

Scientific valid evidence may be acquired from a number of studies capable of supporting or denying a theory about a healthcare treatment, a diagnostic intervention, or about the frequency of occurrence of a health event. However, the translation of scientific knowledge into decisions in healthcare requires methodological expertise and comprehension of the potentials and limitations of each type of evidence. In this chapter, we invite the readers to think more scientifically in their daily practice. We didactically discuss relevant aspects related to the clinical question and study design, and we use this discussion to guide the reader to an improved comprehension of how to use systematic reviews in the context of evidence-based healthcare. Finally, we present some tools and resources to help professionals to search for qualified and preapraised evidence to inform their clinical decisions.

Nowadays, claims about scientific knowledge are not only on the pages of scientific journals, but in newspapers and magazines of wide circulation, in bulletins produced by universities and research institutes, at web sites of the pharmaceutical industries, in collaborative written encyclopaedias, and even in blogs developed by non-scientists. This modern scenario, which is encourage by the online world, probably reflects the nature of the scientific evolution itself: a continuing evolving search for knowledge, and a continuing evolving knowledge. However, the translation of scientific knowledge into decisions in healthcare requires that professionals are

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T.P. Navarro et al. (eds.), *Vascular Diseases for the Non-Specialist*,
DOI 10.1007/978-3-319-46059-8_1

capable of understanding the potentials and limitations of each channel and each type of research. The current amount of information available through these different channels may, for example, amplify research claims that are not based on qualified and rigorous scientific principles. Even when we consider information sources that hold good scientific reputation, the journalistic format may distort the information or part of the scientific rigour. Therefore, the understanding of the fundamental concepts related to how the scientific knowledge in healthcare is developed, and communicated to the public, is essential.

Scientific valid evidence must be acquired from a number of studies capable of supporting or denying a theory about a healthcare treatment, a diagnostic intervention, or about the frequency of occurrence of a health event. Not all evidence is similar, and it may be necessary a critical appraisal and skills in research methods and analysis to assess the quality of the evidence, its accuracy, and practical application [1]. In this scenario, the terminology evidence-based healthcare, or medicine-based healthcare, has become popular. Evidence means the combination of elements used to support the confirmation or denial of a particular theory or scientific hypothesis. Evidence-based healthcare means simply a practice where decisions are guided or informed by these scientific elements. It is about using the evidence effectively to make decision in healthcare instead of relying on the former paradigm [2]:

- Unsystematic observations from the clinical experience
- Clinical practice supported only by the study and understanding of basic mechanisms of disease and physiopathology mechanisms
- Combination of traditional medical training and common sense as sufficient elements to evaluate new test and treatments
- Expertise and clinical experience as sufficient elements to generate valid guidelines for clinical practice

To be translated into practical decisions in healthcare, the evidence has to be relevant and meaningful. A meaningful evidence is based on well-conducted studies with appropriate design to answer the clinical question under investigation. Data analysis and the format of the results presentation are also important factors that may influence the conclusions arising from a particular clinical study. Finally, the conduction and publication of studies by entities deemed to be qualified or respectful does not guarantee research quality *per see*. For instance, many cases of data fabrication and research fraud were conducted in universities with an outstanding reputation, by applauded researchers, and published in high impact journals [3–5]. Studies about drugs and medical devices funded by the manufacturing companies usually lead to more favourable results and conclusions than studies funded by other sources [6, 7], and even animal studies have results exaggerated when sponsored by the industry [8]. This situation is true even when there is a conflict of interest disclosure in the accompanying papers.

Clinical Question and Study Design

Any question addressing a clinical problem has four essential elements: patients (P), intervention (I), comparison (C), and outcomes of interest (O) [9]. This structure is commonly referred as PICO question. For example, one could be interested in the effects of cilostazol (Intervention) in comparison with placebo or other antiplatelet agents (Comparison) in the initial claudication distance (Outcome) of patients with stable intermittent claudication (Patient) [10]. More recently, an additional element has been introduced to the PICO question: the study design (S) [11]. The PICOS question structure is informative because it highlights the fact that not all evidence is appropriate to answer a specific clinical question. In this example, the scientific question was related to the efficacy of a therapy and we would be interested in a randomised clinical trial (an experimental study) where two groups of participants with a disease receiving different treatments according to a randomised allocation are compared. Clinical trials may be regarded as fair, unbiased evaluations, when conducted according to high standard methods [12].

Despite the hype about the substance of clinical trials, they are not the optimal study design to answer all types of clinical questions. This is basically linked to the research method itself: different clinical questions require different types of studies (Table 1.1) [13–16], and the design of the clinical trials is suitable for answering questions about efficacy. Another important question related to the above case study would be the diagnostic accuracy of the ankle-brachial index for the diagnosis of peripheral arterial disease in people with intermittent claudication [17]. This is a fundamental problem, and it is estimated that 85 % of the research is wasted and not useful to answer practical clinical problems because of flaws in research such as wrong question and inappropriate study design [18, 19].

Table 1.1 Study design according to clinical question

Question	Type of question	Study design
What are the benefits of this intervention and its relative safety?	Treatment benefits and common and predicable harms	Experimental studies: randomised controlled trials or *n*-of one trials
What are the harms induced by this intervention?	Treatment harms	Experimental studies: *n*-of 1 trials
		Observational studies: cohort studies, case-control studies, case-series
Is this diagnostic test accurate?	Diagnosis	Cross-sectional or case-control study designs
What will happen if we do not add a therapy?	Prognosis	Cohort studies with incident cases
What is the frequency of a condition or health-related problem in the population? How many people are affected?	Prevalence	Cross-sectional, surveys

Evidence-Based Healthcare and Systematic Reviews

As stated above, the scientific knowledge is always evolving. Our comprehension about the effects of the healthcare interventions, being it a treatment or diagnostic test, is continuing evolving too. However, this oath is frequently ignored and a static piece of information, such as that provided by a product manufacturer or by one published paper, is continuously used to guide decisions.

As a case example, the development of a drug intervention starts with the chemical design and then follows a series of preclinical tests consisted of laboratory and animal experiments. If the drug under investigation succeeds in the preclinical tests, further researches are conducted in human under controlled situations. In this process, the laboratory tests performed in the pre-clinical phase are useful to test the intervention in disease models—animals. The potential efficacy and relativeness safety of the new treatment need to be evaluated in real patients, in a clinical phase constituted of a series of studies named clinical trials. Together, the pre-clinical and clinical data provide relevant answers related to a medical intervention might include a drug, a medical device, or a screening method. Nevertheless, our knowledge about these healthcare interventions is limited at the time they are granted marketing approval. For instance, at the time a drug is approved to be used in real-life situations, only several hundreds to about 3000 volunteers who have the disease to be treated are expected to have been tested [20, 21]. In Europe, from 2000 to 2010, the median total number of patients studied before a drug approval was 1708 [22].

The above numbers demonstrate that the accumulated data related to any intervention is very limited at the time marketing approval is granted. Moreover, to be approved in the United States, there must be adequate data from just two clinical trials [21]. After marketing approval is granted, additional studies and reanalysis of the available published and non-published results may depict more details about the efficacy and harms of the intervention. In addition, the clinical phase of tests continues with observational studies intended to accumulate data on harmful effects. This is essential since clinical trials can only detect frequently and predict harm outcomes, and a complete investigation of all types of harmful effects induced by a healthcare intervention requires the assessment of mainly non-randomised studies [23]. It may now be clear why "no study, whatever the type, should be interpreted in isolation" [24], and why the evidence gathered by all the studies related to a given intervention should be taken collectively to inform healthcare decisions [25]. The research method more capable of accomplishing such a critical overview of the evidence is the so-called systematic review.

A systematic review may be understood as a research undertaken with previous completed studies. Therefore, a systematic review uses an explicit method to collate the primary studies that answer a specific research question [26]. A qualified systematic review may also include a quality assessment of the studies collated, i.e., a judgment of the risk of bias of each included study. A systematic review may or may not include a meta-analysis, which is a statistical method to combine the results of independent studies [27]. Consider the treatment of intermittent claudication

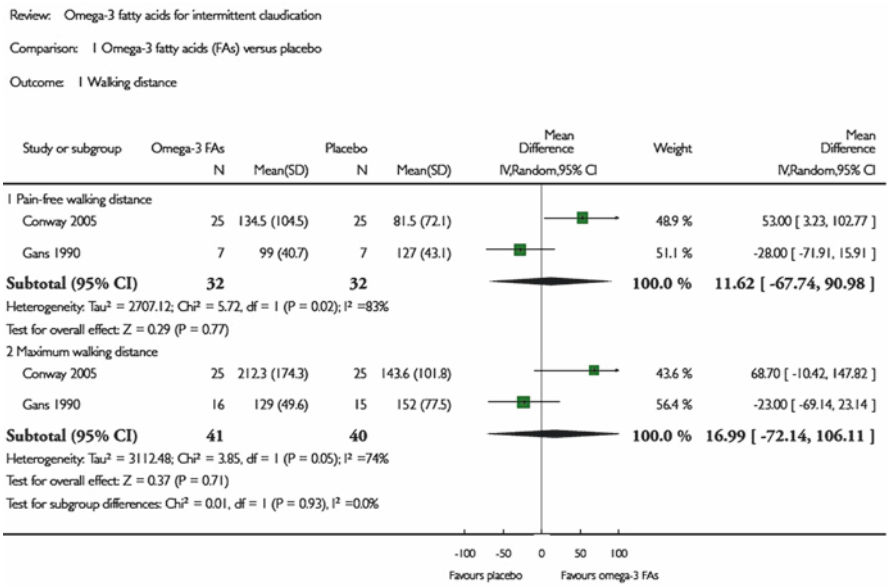

Fig. 1.1 Statistical illustration of two trials demonstrating opposite effects on the pain-free walking distance of omega-3 fatty acid in the treatment of intermittent claudication [28]. The figure presents a graphic name to forest plot. In a forest plot, the point estimate of the result of the individual studies are shown as *squares centred*, and the confidence interval is represented by a *line crossing through the square*. The combined estimate from the meta-analysis and its confidence interval is represented by a *diamond* at the bottom of the graphic [31]. The parallel line crossing the graphic where the mean difference is equal to zero accounts for a result that is equal in the intervention and comparison group. **Reprinted with permission from:** *"Campbell A, Price J, Hiatt WR. Omega-3 fatty acids for intermittent claudication. Cochrane Database Syst Rev. 2013;7:CD003833".*

discussed above. Omega-3 fatty acid [28] has been studied to improve the pain-free walking distance and the maximum walking distance achieved by patients after treatment. Since this is a treatment question, if we search for clinical trials investigating the problem we could find one study published in 2005, which appears to demonstrate that omega-3 is effective to improve the pain-free walking distance and probably an option to also improve the maximum walking distance of individuals with intermittent claudication [29]. However, another trial failed to support the hypothesis that omega-3 was effective to improve either the pain-free walking distance or the maximum walking distance [30]. The combined effect of these trials shows that there is no evidence that omega-3 consistently improves clinical outcomes of patients with intermittent claudication (Fig. 1.1) [28]. If we have not appraised the combined effect of both of these trials in a systematic review, we would be taking decisions informed by biased evidence.

Harms, Not Just Efficacy

Every healthcare intervention will carry a risk—great or small—of inducing harm effects causing injury or disability to patients. Usually, optimistic misconceptions about harms induced by healthcare interventions result in researchers and clinicians inadvertently not taking data on harm in consideration when reporting a study or making decisions in healthcare. Since research reports frequently fail to detail data on harmful effects, the intervention may be erroneously declared safe [32–37]. However, "absence of evidence of harm should not be construed as evidence of absence of harm" [37], and at most we will have data on a relativeness safety of an intervention in these situations. Another issue complicating the evaluation of harms is the several terms used to describe all the harmful events that can be associated to healthcare intervention [23, 38] (Table 1.2). Furthermore, some of the harm effects may be recognised by the healthcare professionals as mild and non-relevant events. Even mild or moderate harmful effects could be of major significance for a treated patient, resulting in poor treatment adherence and in the use of additional medications to treat the harm effect. Drug-induced acute or chronic diarrhoea, which is one of the harms induced by omega-3 and cilostazol [10, 28], can be severe and poorly tolerated [39]. A headache, another harm effect reported by patients treated with cilostazol [10], imposes a recognisable burden on sufferers, including substantial personal suffering, impaired quality of life, and financial cost [40, 41].

The inconsistent report of the frequency of events related to harm effects is another challenge when assessing data on harmful effects. A biased report may

Table 1.2 Terminology of harmful effects

Terminology	Meaning
Adverse event	An unfavourable outcome that occurs during or after the use of a drug or another intervention but is not necessarily caused by it
Adverse effect	An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility
Adverse drug reaction	An adverse effect specific to a drug
Side effect	
This is an old term and should no longer be used because it underestimates the importance of harms associated to healthcare interventions	Any unintended effect, adverse or beneficial, of a drug that occurs at doses normally used for treatment
Harms	The totality of all possible adverse consequences of an intervention

Adapted from: "*Loke YK PD, Herxheimer A. . Chapter 14: Adverse effects. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from http://www.cochrane-handbook.org.*" **and** *"Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. J Clin Epidemiol. 2010;63(5):502–12".*

Table 1.3 Classification of harmful effects according to the frequency of occurrence [42]

Frequency	Classification
>10 %	Very common
>1 % and <10 %	Common
>0.1 % and <1 %	Uncommon
>0.01 and <0.1 %	Rare

Adapted From: "*WHO. Glossary of terms used in Pharmacovigilance 2011 20 March 2015. Available from: http://www.who-umc.org/DynPage.aspx?id=22684*".

often describe a harm effect as rare when it is, in reality, a common effect. The Uppsala Monitoring Centre (UMC), the international drug monitoring programme of the World Health Organization (WHO), suggests a standard classification for the frequency of harmful effects induced by healthcare interventions (Table 1.3) [42].

Finally, it is important to distinguish between harms induced a healthcare intervention and harms caused by professional err. Errors can be prevented by training and by implementing systems that identify and block the error. These systems can be implemented at a institution level, or can consist of simple actions such as avoiding writing a prescription containing abbreviations, symbols, and dose designations that are frequently misinterpreted, to more complex structures and procedures. Harms induced by the intervention itself may not be related to the professional training or experience level, and can only be prevented if we are able to better understand the intervention potential to do more good than harm, or the opposite.

How to Make Decisions in Healthcare

The amount of methodological skills and critical considerations required to evaluate research in healthcare may frustrate any healthcare professional trying to make sense of the evidence at the point of care. Usually, these professionals are already challenged by work overload and cumulative administrative tasks. In this scenario, a few minutes is the time available to answer frequent questions about patient care [43]. The answers are usually built on a "collectively reinforced, internalised, tacit guidelines" [44], meaning that knowledge may be constructed by leaders' opinions and interactions with colleagues, and not based on qualified evidence from research.

To support the availability and the access to qualified evidence, which is relevant to inform decisions in healthcare, there are currently a number of organisations supporting the development of systematic reviews (Table 1.4). In addition, systems of preapraised evidence are being structured with the goal of synthesising the evidence gathered in systematic reviews (Table 1.5). These systems of preapraised evidence are expected to support healthcare professionals to consistently make decisions informed by reliable and accurate evidence. Nevertheless, this goal may only be achieved together with the comprehensiveness of the fundamentals of the scientific knowledge in healthcare, its evolving nature, and the potential flaws that threaten

Table 1.4 Where to find qualified systematic reviews and evidence-based recommendations

Organization	Activity	URL
Cochrane Library	The periodical where the systematic reviews developed under the Cochrane methods are published	http://www.cochranelibrary.com
The Agency for Healthcare Research (AHQR)	The agency, through the Evidence-Based Centre, supports the development of reports using the systematic review methodology	http://www.ahrq.gov/research/findings/evidence-based-reports/index.html
National Institute for Health and Care Excellence (NICE)	NICE offers practical guidance to support effective decisions in healthcare	https://www.nice.org.uk/Guidance
Canadian Agency for Drugs and Technologies in Health (CADTH)	CADTH describes itself as an "independent, not-for-profit organization providing unbiased, reliable information about health technologies"	https://www.cadth.ca/
The Joanna Briggs Institute Library	Repository for publications and information for policy makers, health professionals, health scientists, and others with a practical or academic interest in evidence-based healthcare	http://joannabriggslibrary.org/
Rx for a change	Searchable database containing current research evidence about intervention strategies used to alter behaviours of health technology prescribing, practice, and use	https://www.cadth.ca/rx-change
Health evidence	Searches, compiles, and offer free access to quality-rated systematic reviews evaluating the effectiveness of public health interventions	http://www.healthevidence.org/

Table 1.5 Where to find preapraised evidence

Organization	Activity	URL
BMJ Best Practice	Articles designed to provide a systemic overview of the evidence about therapies available for a given condition	http://bestpractice.bmj.com/
UpToDate®	Overviews of the evidence in all the subareas of internal medicine	http://www.uptodate.com/
Dynamed Plus	Summaries and detailed recommendations based on evidence	http://www.dynamed.com/