
Medical Overtreatment: Friend or Foe?

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Abstract

“Overtreatment” is a neologism coined some 15 years ago to denote medical and surgical interventions that are unnecessary. It is a topical term for an old concept. However, it has rapidly become a shibboleth for those inclined toward finger-pointing and blaming in matters of health policy. As such, it is a “foe” that heats up rather than modulates debate. But if one examines the notion in the context of the contemporary patient-physician dialogue, it is anything but a foe. Overtreatment and its fellow travelers, overutilization and overprescription, face off with contrary notions when a patient contends with the challenge of evaluating any clinical option.

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Introduction

Despite high purpose and sequential moral codes, western medicine has been pummeled for millennia by accusations of doing harm, even causing death, under the banner of therapeutic benefit. There are quacks and mountebanks in prose and poetry who wreaked social iatrogenesis such as portrayed in Robert Burns’ “Death

and Dr. Hornbook” and in Jules Romain’s “Knock” [1]. Thanks to modern regulatory reforms and the plaintiff’s bar, *primum non nocere* has grown teeth. Maleficence transitioned from the unconscionable to the illegal. Attention next turned to the realization that beneficence is a continuum. How much good must be accomplished to garner plaudits? Or the more daunting challenge, how little good should elicit reproach? Anchoring the continuum of beneficence is any therapeutic intervention that is unnecessary or futile. But what is good enough, what is excessive, and who should decide? This is the challenge of the title of this essay.

Overtreatment and the other over-the-top labels rode into the 21st century on the shoulders of the “quality agenda,” a systems approach to rendering care effective and efficient [2]. Osler Peterson pioneered it in the 1950s and deserves far greater recognition for the courage to do so [3]. Peterson joined the staff of the Rockefeller Foundation early in his career, but managed to take lengthy assignments at other institutions. In the early 1950s he was seconded to the fledgling School of Public Health at the University of North Carolina at Chapel Hill. While there, he undertook a series of observational studies that would serve as the foundation for much of his later work. One involved spending days observing the office activities of general practitioners. Armed with a list of domains of performance that Peterson and his colleagues deemed important, the practices were scored for quality. This exercise was carried out despite tremendous variability in

patient mix and practice style. The result was a disappointing score for most practices. For example, Peterson was so convinced that chest percussion was an indication of the quality of the physical examination that nonperformance earned demerits for the majority of the practices. The scores and the scoring were met with resentment, criticism, and outcry. Peterson abandoned this approach to measuring quality, calling for observations on defined populations, often inpatients, with particular diagnoses.

Peterson's epiphany coincided with the enactment of laws regulating the pharmaceutical and device industries. The notion that the practice of medicine was characterized by tremendous variability in patient mix and practice style was subjugated to the definition and measurement of efficacy. The establishment of efficacy is a deductive exercise that holds the randomized controlled trial (RCT) as grail. It is an exercise that generally relies on targeted patient populations chosen to minimize variability and thereby maximize the likelihood of detecting an effect in a particular subset. The practice of medicine had a new measurement of quality, the reliance on interventions that were bolstered by the demonstration of a statistically significant benefit in a selected patient population. No pharmaceutical is licensed in North America or Europe without passing muster to this degree. The standard for licensing devices is less stringent. The standard for procedures still relies on peer review.

This essay will consider only licensed interventions, meaning there are sufficient data for efficacy to convince a regulatory agency. Discussions about off-label use or about interventions that have not been studied or cannot be studied are a separate but equally important discussion that merits another essay. The licensing process demands at least one "licensing trial," an RCT that demonstrated a statistically significant positive outcome in a defined population. The regulatory agency is also charged with assuring that the intervention is not likely to be harmful. The licensing trial would provide an elegant definition of "quality" were it not for provisos to the notion of a positive result that are critical in informing clinical decisions.

While licensure speaks to the probability of a difference between an intervention and a comparator in a defined study population, it may not speak to the utility for a given patient. That is a leap that demands consideration of the size, reliability, and generalizability of the effect, the likely downsides of the intervention, out-of-pocket expenditures, preconceptions, and other aspects that influence the degree to which a given patient might value the intervention. It is a leap that requires a conversation between the patient and the prescribing practitioner. Con-

ducting this conversation (and the elicitation of the narrative of illness that proceeded) is the essence of the treatment act. It is an exercise fraught with a tendency for linguistic determinism [4].

The role of the physician in the conversation relates in part to the penetrability of the stochastic considerations. Stochastic considerations may or may not be determinative, depending on the patient's degree of risk tolerance. Whether stochastic considerations reach the threshold of offering meaningful utility is the patient's judgment. If the benefit does not meet this criterion, why bother with it? The degree to which the patient-physician dialogue serves this end is the degree to which healthcare becomes reality-based. One dialogue might result in the patient's decision to accept a particular intervention, whereas another dialogue might lead to rejection of the same intervention. Imprecations such as over- and undertreatment do not pertain; they reflect the relative values of others. When the patient is stymied by equipoise, the query "What would you do, doc?" is no longer appropriate. The query for the 21st century is "What would you do, doc, if you were me?" [2].

The Patient-Physician Consultation

The name of the dialogue between a patient and a physician in response to the patient's needs for care has revelatory semiotics. Physicians are wont to speak of "seeing patients" as in "I saw 10 patients on rounds this morning." We are also comfortable denoting the event as an "examination." There are other terms that similarly objectify the patient as a clinical challenge rather than as someone seeking clinical insights they were incapable of defining on their own. I have never been comfortable with such terms or the disparity in power they signify. But now, in the 21st century, such terms do a disservice to both patient and physician. We need a term that levels the playing field because, finally, it can be leveled. The clinical dialogue is a consultation between patient and physician with the same goals as a consultation between physicians. The patient-physician consultation is to be informed by integrating experience, presupposition, goals, and evidence.

While I am at it, let us decry the proclivity of health administrators and policy wonks to label physicians as "providers" and patients as "units of care" or the like. These are co-opted from industrial engineering. Physicians and allied health professionals are not providers; they are practitioners of the healing arts. And patients are

not clients or consumers, let alone units of care; they are human beings in need of caring. Why else would they choose to be patients? The patient-physician consultation cannot be well served by “physician extenders,” be they breathing or not.

Much has been written about the role of evidence in informing clinical decisions. Much that is written takes, as a given, that the weight of the “evidence” should be very influential, if not determinative. The result is some 10,000 “guidelines,” each purporting to obviate the need for further discussion. The inconsistencies in conclusions about most therapeutic options often reflect inadequacies in the scientific data, particularly in instances where suggestions of limited therapeutic efficacy are extracted from large data sets [5, 6]. The inconsistency in a given recommendation over time reflects the small-group psychology of the committee charged with coming to a conclusion [7]. The typical braggadocio of the committees pronouncing their “recommendation” despite the vagaries of the metrics can often be ascribed to conflicts of interest on the part of participants. Certainly, many an expert enjoys an equity position that aligns with their conclusion [8, 9], and many a study suffers from the biases inherent in industry sponsorship [10]. However, few experts see themselves as misanthropes in this regard. Rather, the consensus of the committee reflects the values and preconceptions its members bring to the task of analyzing flawed data sets. Hence, one committee’s assessment that a particular trial is fatally flawed can stand in contradistinction to the assessment of another committee that considers the same trial exemplary. That is why one committee’s assessment of overtreatment is another’s of standard of care [11]. That is why the lay and clinical literature suffers as a reliable source of information. Today the “evidentiary basis for clinical practice” is a contentious cacophony driven by market considerations that threaten its ethical basis.

Missing in the guideline exercises are the values of patients. Of course, bringing a patient or a group of patients or an “average” patient to the committee’s table is fatuous. Given the flawed nature of most of the metrics and the reliance on the values of the evaluators, no one should use a “guideline” as a guidepost. The “guideline” is best for identifying whether the science is simply too inadequate to be informative. It may be sufficient to conclude that the putative therapeutic effect offers too little for any patient to have a reasonable expectation of utility. Such an intervention is without clinically meaningful benefit. If there is some likelihood of benefit, the determination of the magnitude of that likelihood and of its relevance to a par-

ticular patient reverts to the patient-physician consultation. Anyone who is ill enough to seek guidance and comfort from a physician deserves to interact with a medical practitioner who can be trusted to conduct a patient-physician consultation specifically and solely for that patient. Guidelines may pertain, but are not determinative.

The Patient-Physician Consultation in Geriatrics

Patient-physician consultations in gerontology are advantaged by the wisdom of the aged. Seldom is a delusion of immortality intrusive. Seldom can the context of the activities of daily life and the role of “community” be excluded. Gerontology practice demands a conversation about the age-appropriateness and context-reasonableness of options [12]. So, too, do consultations in other, maybe in all realms of medicine, but gerontology is anchored in the course of life, not in intermittent or remittent events. In geriatrics, “lifesaving” connotes trying to make it likely that any patient will live out life as fully as possible, not that every intervention is to be ranked on a scale of interventions leading up to cardiopulmonary resuscitation. Some elderly understand this, but others and many who are in their caring community do not. They have been pummeled by marketing, by inappropriate health journalism, and by the common sense, so that most Americans of all ages are pitifully medicalized and Europeans are hell-bent to find seats on the American bandwagon. The fine details may differ, but the need to cut through the misinformation and misconceptions is at least as pressing when the patient is elderly and the doctor is a geriatrician as it is for other clinical settings.

Certainly, the patient-physician consultation in geriatrics includes a component that is “scientific.” It also includes caring for and about the person who chose to be a patient in order to consider options in a trustworthy and penetrable fashion. In the recent past, the first component came to supersede the second as a matter of principle. It is now clear that this principle is untenable. For the sake of argument and of illustration, let us restrict our further considerations to septuagenarians who are enjoying this stage of life. Of course, they are coping with episodic morbidity as we all do at every stage of life. At this stage, coping is tested frequently by musculoskeletal discomfort and by the realization that so many changes in habitus and function are age-appropriate and not diseases [13]. Thanks to a robust literature in community epidemiology, we know that most are coping so well most of the time that they have no need to become patients.

The science that informs the geriatric consultation is more limited than that for younger adults. A population of septuagenarians abounds in all sorts of comorbidities and in polypharmacy. This tests the mettle of the aged and the acumen of the geriatrician, but this variability does not often test the intellect of biostatisticians who would rather seek efficacy in populations that are not so complex. Hence, we have relatively little data on septuagenarians, and neither do regulatory agencies. But we do have an understanding of their time of life to inform the conversation. We know that death and dying has an immediacy that few younger patients experience. A good “outcome” for our patients is arriving at a ripe old age still smiling. We are less concerned about their disease burden, which is substantial, or which disease proves their reaper. We understand that the most appropriate cause of death should be “It was her/his time” [14].

Medicine is not a science, it is a philosophy informed by science. Today reliable and valid science is so robust that we have the temerity to speak of “evidence-based medicine” (EBM). Nonetheless, medicine remains and will always be a philosophy informed by science. As Benjamin Djulbegovic and Gordon Guyatt say, “EBM can be defined from an epistemologic point of view as a set of principles and methods to ensure that population-based policies and individual decisions are consistent with all the most credible evidence while relying on both type 1 and type 2 cognitive processes to weigh the tradeoffs involved in alternative courses of action” [15]. Furthermore, these analytical and intuitive cognitive processes must be honed to serve the particular elements of each clinical and policy decision [16].

The Imperious p Value

To serve this ethic, we first need to level the playing field. There are abuses of analytics hiding in the clamor of EBM that overwhelm the intuitive cognitive processes.

The Lottery Sophism

There is a difference between an outlier in an RCT and a lottery winner, a distinction that many cannot get their head around. But it is not simply because people cannot understand; it is because people are fed a diet of analytics designed to obfuscate. The RCT is designed to test a null hypothesis, i.e., that there is no statistically significant difference between a particular intervention and some comparator, the control. Individual differences dictate that there will be a range of outcomes in both groups. By sta-

tistically different difference, one is seeking a difference in the range of outcomes that would not happen by chance more than 5% of the time ($p < 0.05$). Such a difference is usually declared to be a “positive” result. This standard cutoff has an interesting history, but it is entirely arbitrary. The conclusion of positivity is in the eyes of the beholder, and for us the beholders are the participants in the patient-physician consultation. The statistically significant difference is clinically meaningless unless one knows the magnitude and frequency of the difference that is detected. If it is a very infrequent and/or minor effect, it can be much ado about nothing that is worth our while. That is a hard sell in our times when people are willing to purchase lottery tickets hoping for a very infrequent “win” – and someone will win. But an RCT is not a lottery. It asks whether you are more likely to have an infrequent outcome if you were subjected to the test intervention than if you were subjected to the comparator intervention. Hence, it is asking how much less likely you are to win this RCT “lottery” if you did not buy the ticket. That is the question one should ask when the data suggest that an occasional benefit, the outlier, occurs more frequently in the treatment arm of the study than in the control arm. Is this intervention worse than doing nothing or doing less [17]? There may be some debate as to the answer, but there is no debate as to the appropriateness of the questioning for numerous medical [18] and surgical [19] options.

Mind-Boggled by Meta-Analysis

If you enjoy analytics, meta-analyses are fun. They are usually undertaken when faced with a number of published RCTs on the same agent with varying outcomes. The default is to be influenced by the trial that seems most compelling for whatever reason. A meta-analysis tries to bolster a subjective conclusion by extracting meaning from all the trials, even those that seem less compelling. This requires weighting the trials as to how close their methodology approaches some ideal and combining the data accordingly. Meta-analyses abound not only in the literature, but on the tongues of trainees and practitioners. Of course, both the definition of ideal methodology and the degree to which the trials approach the ideal are in the eyes of the beholder. It is not a surprise that industry-supported meta-analyses tend to find more positivity than government-supported exercises [10]. The biostatisticians have done yeoman’s work trying to make the most of meta-analysis. But seldom is one published when the literature supports a conclusion of a compelling, frequent, large benefit. My assumption whenever I see a meta-analysis is that it is much ado about too little to be clinically meaningful.

Not All “Positives” Are Created the Same

Occasionally, an intervention hits a home run. That is when many that are treated experience a dramatic benefit most of the time. Usually, the benefits fall far short of this “no-brainer.” Looking for the less dramatic benefit requires large, prolonged, expensive trials in quest of a statistically significant outcome. Pharmaceutical firms often contract with contract research organizations for the performance of these trials, an arrangement that is inherently biased toward the contract research organization’s finding a result that will not “bite the hand that feeds you.” Such trials lend themselves to all sorts of data massaging and torturing and all sorts of liberties in the presentation of the results. Take AstraZeneca’s herculean JUPITER trial [20] as an object lesson. Six months before its publication, AstraZeneca announced it had stopped the trial early, at 1.9 years, on the advice of its oversight committee because an interval analysis of the data detected a 56% reduction in a composite of cardiovascular outcomes. The stock market took notice immediately and, in no time, rosuvastatin (Crestor) was a blockbuster drug. JUPITER screened 90,000 people to enroll 18,000 well people with “normal” cholesterols and high high-sensitivity C-reactive protein values in 1,300 centers around the world. The event rate for volunteers taking Crestor was 0.77 persons for every 100 persons treated in a year. The event rate for volunteers on a placebo was 1.36. That is the 56% relative reduction. It is but a 0.59 absolute reduction in the event rate, i.e., less than 1 person in 100 has a demonstrable cardiovascular benefit in a year of exposure to Crestor. If one parses the composite outcome, we learn that the best we could hope for is to treat about 400 people for a year to spare one a nonfatal heart attack. There are many lessons and caveats from JUPITER [8] which generalize to all discussions about the primary prevention of cardiovascular disease at any age. All are relevant any time a geriatrician engages in a patient-physician consultation regarding risk reduction. Nearly always, extricating clinical meaningfulness from the hype requires the physician to get into the weeds of the study, by Jove.

Geriatrics at the Cutting Edge

I began this essay referring to Robert Burns’ “Death and Dr. Hornbook” and Jules Romain’s “Knock” as if medicalization, iatrogenesis, and social iatrogenesis were reprehensible history. If only they were. Furthermore, thanks largely to advances in the structure of much of western society since World War II [13], the elderly are

targeted for all, and gerontology has the burden for interceding on their behalf. There is many a mainstay of contemporary practice that begs for the patient-geriatrician consultation set forth above. Some are very much in the public eye thanks to the visibility of the controversies. Everyone is aware that policies of screening any cancer in working-age adults are surrounded by controversy for very good reasons. For the geriatric consultation, the discussion is framed in terms of whether extirpating an early cancer will alter the patient’s age of death given the many diseases and processes that compete for “all-cause” mortality. The geriatrician will not have to spend much time in the weeds to be able to arm the patient with sufficient epidemiology to inform the patient’s judgment.

The same holds for cardiovascular risk reduction. In fact, that is getting easier. Even the contrived benefits suggested by the authors of the JUPITER trial do not pertain to the elderly population for whom very long-term benefits are less relevant. Furthermore, there is a suggestion that prescribing statins to the elderly may make it less likely that they will reach their ripe old age [21]. The epidemiology of cardiovascular risk reduction is a hotbed of controversy beyond lipid levels. The debates surrounding the definition and treatment of “essential” hypertension date back several generations and have been enflamed recently by the SPRINT trial [22]. This NIH-supported trial was funded at the urging of an advisory panel and carried out by a “research group” in which many of the nation’s leading hypertension experts participated, many with conflictual relationships with pharmaceutical firms. For some reason it was felt that systolic hypertension in the elderly was undertreated with the conservative regimens supported by earlier trials such as the SHEP trial. SPRINT got aggressive, but also methodologically sloppy both in the fashion in which blood pressure was measured and the fact the trial was stopped early because the oversight committee was impressed with a small benefit from aggressive treatment that outweighed the harms. Stopping trials early for small benefits, as opposed to small harms, is a troubling and generally rejected option. Small differences come and go during these large and prolonged trials. If you wait for one in the direction you favor, you will be rewarded, but likely by a spurious inference. The European Society of Cardiology was not impressed with SPRINT’s result. The American College of Physicians was also unimpressed, but the American Heart Association and the American College of Cardiology used the results to change the definition of hypertension such that nearly half American adults and more than half American elderly would qualify [23]. The geriatric consultation re-

garding the treatment of hypertension will promote gray-ing of both the patient and the physician [24].

Contentious consultations regarding cardiovascular morbidity and mortality are not restricted to risk reduction. Interventional cardiology is on the cusp of ignominy that neither Robert Burns nor Jules Romain could have envisioned. There are multiple trials of various forms of coronary artery stenting in various clinical settings, including the STEMI presentation, that cannot demonstrate an advantage for the patient [8, 25]. There are sham-controlled trials of coronary artery stenting and bypass surgery for stable angina that should sound the death knell for this therapeutic approach [26], but probably will not in view of the magnitude of intellectual and fiscal investment mobilized to push back. Thus, it reverts to the patient-geriatrician consultation. The consultation regarding the “left main disease” rationale for coronary artery stenting and bypass needs to contend with the low (3%) yield on arteriography and the substantial mortality and morbidity of the procedures in the elderly.

In fact, the elderly patient-geriatrician consultation has moved center stage for its complexity and its importance. So much that is now routinely considered and often prescribed should not be. The scientific literature has an important debate on the utility of influenza vaccination in the elderly. Arthroscopic surgery for knee pain in the elderly [27], surgery for degenerative “lumbar spinal stenosis” [28], and even reflexively admitting the elderly to intensive care units [29] call for consultations.

The Geriatric Consultation on the Moral High Ground

This is a very short list of contentious, convoluted consultations that often engender cognitive dissonance for the patient and for the physician. For starters, there are challenges just in defining, let alone diagnosing, osteoporosis, type 2 diabetes, diverticulitis, mild cognitive impairment, affective disorders, nonvalvular atrial fibrillation, mild heart failure, and skin cancers. Once through the diagnostic gantlet, there is the high calling of collaborating with a patient regarding treatment options. These are clinical exercises that demand human interactions and noble intent. None of this can be well served by reliance on computerized mining of large data sets; no algorithm can encompass human variability manifest as idioms of distress that include surrogate complaints. This is why we need physicians. Treatment itself is seldom more than a technical challenge, if it is a challenge at all. It is the treatment act that is the high calling.

That said, we are rapidly getting mired in the inadequacies of the scientific method. It is difficult to collaborate regarding options if the objective basis for making decisions is unreliable [30]. And that difficulty is compounded if patients and physicians are burdened with preconceptions to the contrary [31]. The reflex to “act” rather than to “reflect” explains the tendency to prescribe interventions that are so unlikely to provide benefit for a particular patient that their prescription is fatuous. There is no moral justification for licensing drugs and devices based on the demonstration of a statistically significant degree of efficacy that is clinically marginal if not meaningless. Furthermore, there is no moral justification for assuming that marginal efficacy demonstrated in one subset of patients will prove less marginal in another. And there is no reason to expect that one can go fishing in the highly confounded data generated after licensure for the elusive reliable clinical inferences as to effectiveness. The quest for comparative effectiveness in these data sets assumes that something really works. If not, the exercise may devolve to comparative ineffectiveness research.

There is a solution to this quagmire. Biostatistics offers methodologies that move the decision for licensure from efficacy based on rejecting the null hypothesis at the $p < 0.05$ level of confidence to a level of confidence that imputes a degree of clinical meaningfulness [32, 33]. Many a marginal and “me too” option would disappear from the current therapeutic menu and would not be replaced by options of similar ilk going forward. The pharmaceutical, device, and “healthcare” [8] industries would trade size and profitability for ethic. But the time in the clinic will be dramatically unburdened by the need to dismiss the irrelevant. After generations of clinical decisions based on the well-meaning application of inadequate information, often colored by hubris, we are in a position to promote a clinical consultation that is enlightened and enlightening, resulting in a rational treatment act that eschews rationing.

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References

- 1 Bamforth I: Knock: a study in medical cynicism. *Med Humanit* 2002;28:14–18.
- 2 Hadler NM: *By the Bedside of the Patient. Lessons for the Twenty-First-Century Physician.* Chapel Hill, UNC Press, 2016, pp 89–99.
- 3 Peterson OL: Medical care: its social and organizational aspects. Evaluation of the quality of medical care. *N Engl J Med* 1963;269:1238–1245.
- 4 Barsky A: The iatrogenic potential of the physician's words. *JAMA* 2017;318:2425–2426.
- 5 Lenzer J, Hoffman J, Furburg C, Ioannidis J; Guideline Panel Review Working Group: Ensuring the integrity of clinical practice guidelines: a tool for protecting patients. *BMJ* 2013;347:f5535.
- 6 Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, Loke Y, Vohra S: Quality of reporting in systematic reviews of adverse events: systematic review. *BMJ* 2014;348:f7668.
- 7 Saver BG: A piece of my mind. Should C be a passing grade for the USPSTF? *JAMA* 2015;313:465–466.
- 8 Hadler NM: *The Citizen Patient. Reforming Health Care for the Sake of the Patient, Not the System.* Chapel Hill, UNC Press, 2013, pp 1–245.
- 9 Rothman D: Leadership by example: saying no to health industry board membership. *BMJ* 2015;351:h5065.
- 10 Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L: Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2017;2:MR000033.
- 11 Ransohoff DF, Sox HC: Clinical practice guidelines for colorectal cancer screening. New recommendations and new challenges. *JAMA* 2016;315:2529–2531.
- 12 Williams MD, Hadler NM: The illness as the focus of geriatric medicine. *N Engl J Med* 1983;308:1357–1360.
- 13 Hadler NM: *Rethinking Aging.* Chapel Hill, UNC Press, 2011, pp 1–250.
- 14 Hadler NM: A ripe old age. *Arch Intern Med* 2003;163:1261–1262.
- 15 Djulbegovic B, Guyatt G: Evidence-based medicine and the theory of knowledge; in Guyatt G, Meade M, Cook D (eds): *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice.* Boston, McGraw-Hill, 2014.
- 16 Djulbegovic B, Elqayam S, Dale W: Rational decision making in medicine: implications for overuse and underuse. *J Eval Clin Pract* 2017, Epub ahead of print.
- 17 Ioannidis JPA: How many contemporary medical practices are worse than doing nothing or doing less? *Mayo Clin Proc* 2013;88:779–781.
- 18 Morgan DJ, Dhruva SS, Coon ER, Wright SM, Korenstein D: 2017 update on medical overuse: a systematic review. *JAMA Intern Med* 2018;178:110–115.
- 19 DuBois JM, Chibnall JT, Anderson EE, Walsh HA, Eggers M, Baldwin K, Dineen KK: Exploring unnecessary invasive procedures in the United States: a retrospective mixed-methods analysis of cases from 2008–2016. *Patient Saf Surg* 2017;11:30.
- 20 Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;329:2195–2207.
- 21 Curfman G: Risks of statin therapy in older adults. *JAMA Intern Med* 2017;177:966.
- 22 Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT Jr, Pajewski NM; SPRINT Research Group: Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥ 75 years: a randomized clinical trial. *JAMA* 2016;315:2673–2682.
- 23 Pignone M, Viera AJ: Blood pressure treatment targets in adults aged 60 years or older. *Ann Intern Med* 2017;166:445–446.
- 24 Goodwin JS: Decreasing blood pressure in older patients. *JAMA Intern Med* 2018;178:100–101.
- 25 Hadler N: The end of the era of coronary angioplasty. <http://thehealthcareblog.com/blog/2013/10/13/the-end-of-the-coronary-angioplasty-era/>.
- 26 Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewiczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP; ORBITA investigators: Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391:31–40.
- 27 Siemieniuk RAC, Harris IA, Agoritsas T, Poolman RW, Brignardello-Petersen R, Van de Velde S, Buchbinder R, Englund M, Lytvyn L, Quinlan C, Helsing L, Knutsen G, Olsen NR, Macdonald H, Hailey L, Wilson HM, Lydiatt A, Kristiansen A: Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ* 2017;357:j1982.
- 28 Wessberg P, Frennered K: Central lumbar spinal stenosis: natural history of non-surgical patients. *Eur Spine J* 2017;26:2536–2542.
- 29 Guidet B, Leblanc G, Simon T, Woimant M, Quenot JP, Ganansia O, Maignan M, Yordanov Y, Delorme S, Doumenc B, Fartoukh M, Charrestan P, Trognon P, Galichon B, Javaud N, Patzak A, Garrouste-Orgeas M, Thomas C, Azerad S, Pateron D, Boumendil A; ICE-CUB 2 Study Network: Effect of systematic intensive care unit triage on long-term mortality among critically ill elderly patients in France: a randomized clinical trial. *JAMA* 2017;318:1450–1459.
- 30 Carter SM, Rogers W, Heath I, Degeling C, Doust J, Barratt A: The challenge of overdiagnosis begins with its definition. *BMJ* 2015;350:h869.
- 31 Rosenbaum L: The less-is-more crusade – are we overmedicalizing or oversimplifying? *N Engl J Med* 2017;377:2392–2397.
- 32 Hadler NM, Gillings DB: On the design of the phase III drug trial. *Arthritis Rheum* 1983;26:1354–1361.
- 33 Manski CF, Tetenov A: Sufficient trial size to inform clinical practice. *Proc Natl Acad Sci USA* 2016;113:10518–10523.