

# Distinguished Lecture Given at the Opening of the 5<sup>th</sup> International Meeting on Aortic Disease, Liège, Belgium (September 15, 2016)

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## Key Words

**Aortic aneurysm • Writing and publishing • Clinical trials**

It is my pleasure to give this opening talk for the fifth edition of the International Meeting on Aortic Disease – which, as I've said before, is my favorite meeting. As many of you know, it began in 2008 as a tribute to Liège's eminent vascular surgeon and scientist Ray Limet, and has recurred every other year since. It remains about science rather than marketing, and has the right mix of talks, breaks, and social events to get to know colleagues worldwide. I was honored to be invited to give this talk, but also a little worried, especially seeing it billed as a "distinguished lecture". This seemed to call for something like wisdom, a commodity that's always in short supply (as you will soon see), so I intend to borrow liberally from others toward the end. Anyway, I will talk for a while and you can decide how distinguished you think it is.

I am especially honored to be addressing this audience because, unlike most of you, I was not trained in aortic diseases. I must have had a lecture on the topic in medical school, but I don't remember it. Instead I trained as an internist and developed an interest in clinical research (again with no training!) after joining the faculty at the Minneapolis Veterans Affairs (VA) Medical Center. Our general internal medicine group was interested in research methodology and preven-

tive medicine – smoking cessation, flu shots, prostate cancer screening, and the like.

I was looking for a research topic when the January 1986 American Cancer Society journal *CA* arrived in my mailbox listing the top 15 causes of death in the United States, and I was surprised to find aortic aneurysm among them. All the other "top 15" had societies and campaigns dedicated to their eradication, whereas this one seemed to be just sitting there waiting for someone to take an interest. About that same time I also came across Jack Collin's November 1985 editorial on "Screening for Abdominal Aortic Aneurysms" [1], inspired by an abstract by Twomey from the year before. These revelations prompted me to do an aneurysm screening project in our clinic, which was published in 1988 [2].

My next thought was to do a randomized trial of screening for abdominal aortic aneurysms, but when I thought about it more, it seemed to me that there was a serious problem. Sudden deaths without autopsy, which are quite common and usually not due to aneurysms, would be much more likely to be attributed to aneurysm rupture in the screened group (where many aneurysms would be diagnosed) than in the control group (where there would be fewer known aneurysms), which would have the effect of hiding any true reduction in rupture mortality from screening.

I tried to find ways to deal with this problem in a 1990 article in the *Journal of Clinical Epidemiology*



[3], but none of them were feasible. The only reaction I ever got to that article that basically explained why a randomized trial of aneurysm screening could not be successful was years later from my friend Alan Scott, the principle investigator of the two British aneurysm screening trials that changed the world. His comment was "I'm glad I didn't see it".

Another problem for me doing a screening trial was that unlike in other countries at that time, the US already required consent from everyone first, resulting in much more work and cost and many cross-overs. The four trials that were actually conducted, all outside the US, just randomized a population list and invited half to screening, with the controls never knowing they were being studied.

Because a screening trial was impractical for me, a 'repair of small aneurysms' trial seemed like the next best thing. If repair of small aneurysms was beneficial, it would help make a strong case for screening. If it was not beneficial, the cost-effectiveness of screening would be greatly improved by avoiding repair of all those small aneurysms. Besides, a 'repair of small aneurysms' trial addressed a decision that was interesting enough in its own right. You have a common cause of death that lies in wait, easily detectable for many years, but with a treatment that is itself risky and must be applied selectively.

During the Wall Street Journal's 2004 Pulitzer Prize-winning series on aortic aneurysm, one of the reporters asked my opinion of a surgeon's comment that deciding whether to repair an aortic aneurysm was like deciding whether to repair a defective hose in an airplane engine before you took off – meaning that you would be crazy not to. I thought the analogy should take account of a few other things, that is: aneurysm repair itself offered a risk of 'crashing', and its result, a synthetic graft, was not quite 'as good as new'. I suggested a revised analogy of whether to repair the airplane engine hose with your jacket sleeve after turning the engine off in mid-flight. The reporter decided to steer clear of airplane analogies, but you can't help being fascinated by a clinical problem like this!

In 1990, a new colleague joined our group from the Boston VA, where her mentor was chief of the VA Cooperative Studies Program and she had a Cooperative study approved for planning. This provided me with encouragement (and a template!) to submit a letter of intent for the Aneurysm Detection and Management (ADAM) study

to VA Cooperative Studies that year. In 1992, as we were going before the evaluation committee, the Society for Vascular Surgery recommended elective repair of all abdominal aortic aneurysms 4.0 cm or larger, which raised the stakes and the study was approved and funded.

After that I had to take long phone calls from vascular surgeons telling me how unethical the study was for delaying surgery in the surveillance group. However, once we got going, a major VA medical center refused to participate because they considered repairing 4.0 cm aneurysms to be unethical, so at least we had equipoise of outrage!

As you know, the results of the two small aneurysm trials, ADAM and UK Small Aneurysm Trial (UKSAT), showed no benefit from repairing abdominal aortic aneurysms smaller than 5.5 cm in diameter. While no one has challenged the validity of these findings, it has been a disappointment to me that, to this day, many (and in my own country, perhaps most) of the abdominal aortic aneurysms repaired are smaller than 5.5 cm. Various justifications for this practice have been proposed, but the reasons are not valid and don't stand up to scrutiny. It seems that people just want to repair small aneurysms, regardless of the data showing that it is not good for the patient. This has surprised me, because all the vascular surgeons I know are so profoundly dedicated to their patients' welfare in every other way.

For me, after the ADAM trial, one large study led to others, including the Natural History of Large Aneurysms Study, published in 2002 [4] and the VA Open Versus Endovascular Repair (OVER) Trial, published in 2012 [5]. My current trial will sound less "vascular" by your reckoning – a comparison of major cardiovascular outcomes after treatment of hypertension with chlorthalidone or hydrochlorothiazide (2 similar diuretics) using a new low-cost centralized design [6]. This and similar designs used by ADAPTABLE, the NIH's first National Patient-Centered Clinical Research Network trial on aspirin dosing, and TASTE, a recent Swedish Registry trial on thrombus aspiration, are worth your attention as they chart a path to a future of less expensive randomized trials, on which we will increasingly depend.

Anyway, for me this amounts to about 30 years in clinical research and leading large trials, mostly on abdominal aortic aneurysms, and I'd like to finish up by sharing a few things I've learned over that time,

especially in hope of benefitting the younger investigators.

First, ask a good question. The best questions can be stated clearly and are easily understood by non-experts. As one author put it, "Until you can explain your study to the janitor and see his eyes light up, you are not ready to start" [7]. I like to look for things that are widely believed or are enshrined in guidelines, but that I think are probably wrong. And I am not the only who thinks this way. The pathologist Paul Broca said "The least questioned assumptions are often the most questionable." Physicist Richard Feynman said "Learn from science that you must doubt the experts." Playwrite George Bernard Shaw said "All great truths begin as blasphemies." And Alvan Feinstein, one of the founders of clinical epidemiology, said "the agreement of experts has been a traditional source of all the errors that have been established throughout medical history" [8]. There are still plenty of widely accepted "facts" out there that are not true, and you probably each know of some – I encourage you to point your research in that direction.

As principal investigator of your own study, you are the one who must keep pushing it forward and who knows the big picture so well that you can ensure that any changes to your design don't cause worse problems than they solve. While few people can actually stop you, many can slow you down. In particular, anytime that you assume that some part of your study is going well because someone else is looking after it, you may be headed for a surprise. I have found that if the principal investigator is not keeping an eye on it personally, it probably isn't getting done. Sitting around the table (real or virtual), be sure you have done your homework, avoid groupthink, provide your own honest independent assessments, don't overstate your conclusions, and if you have nothing to say, say nothing.

I'd also like to say a few words about writing. After all, that's all there is in the end. Always keep the eventual journal article in mind while you plan your study, and keep the possible reviews and letters in mind while you write the journal article. Never write a sentence you can't defend – it will likely turn up in quotes in one of those reviews or letters. And don't forget to write the article! Most presented abstracts are never published as manuscripts, in most cases because they are never submitted as manuscripts [9]. I submit the meeting abstract after the paper is written – the paper is no harder

that way but the abstract is much easier and more accurate, and actually agrees with the article! And don't have someone else write your paper! There were surgeons in our hospital who would have their secretary write their articles! Do your own word processing – it's much better than the old days of typewriters – you can throw ideas and content into the document throughout the whole design and study period, and edit it later.

Best-selling author John Grisham said "The best advice I ever got was to write at least one page a day. Until you write a page, nothing is going to happen." In a study by Boice, those who set aside 15-30 minutes a day to write were more likely to obtain academic promotion than were binge writers [10]. You can start the writing session painlessly by going over what you've already written. As US Supreme Court Justice Louis Brandeis noted "There is no good writing, only good re-writing."

After double-checking your data, stand by your results, even if they refute your bias and everyone else's. As Isaac Asimov put it, "The most exciting phrase to hear in science, the one that heralds the most discoveries, is not "Eureka!", but "That's funny...". Don't fall into the mistake John Kenneth Galbraith warned of when he said "Faced with the choice between changing one's mind and proving that there is no need to do so, almost everyone gets busy on the proof." The best way to stay unbiased is to stay unbought, so beware of financial relationships with industry. Here I repeat Upton Sinclair's observation that "It is difficult to get a man to understand something when his salary depends upon his not understanding it."

Some authors like to write long and rambling discussions, stating their favorite opinions on a variety of topics. This never helps get a manuscript accepted and can hurt, especially if the reviewer has different opinions or you overstate your findings. Let the data speak for themselves, and remember your findings don't 'prove' anything, they agree with or don't agree with some hypothesis, thereby contributing to the collective body of knowledge. Dean Hess wrote [11]: "The purpose of research is to discover and not to prove. It is easy to fall into the trap of designing the study to prove your bias rather than to discover the truth".

Also important is what you do with the paper when you get it back from the journal. To quote myself from a 2006 talk: "While it is often necessary to write a strongly worded letter, it is rarely necessary to mail it". The fault

is always with the author, as in “I may have failed to convey...”. Learn to handle rejection; we only count the victories on our résumés anyway. Winston Churchill said “Success is the ability to go from one failure to another with no loss of enthusiasm.” A rejection can also be the beginning of a dialog (and several editors have said so in print). I have had five flat-out rejections later accepted by the rejecting journal.

Another thing I have learned is that, once you pass the age of 50, nothing is more satisfying than mentoring junior investigators, and doing so strictly for their professional advantage, not your own. Of course, only in that way do you really benefit in the ways that count. Erik Erikson, a successor to Piaget in sorting out what makes us mentally healthy throughout our lives, talked a lot about this. His 7<sup>th</sup> stage of life he termed: Generativity vs. Stagnation. Generativity is described as “primarily the concern in establishing and guiding the next generation” and he speaks of “the only happiness that is lasting: to increase, by whatever is yours to give, the goodwill and higher order in your sector of the world” [12]. Many of you already know from experience how satisfying mentoring can be.

Finally, I’ve learned that we should remember those who got us here. In the case of IMAD5, that can only mean our conference director, Natzi Sakalihan. Ralph Waldo Emerson said that “An institution is the lengthened shadow of one man”, and if

the institution is the International Meeting for Aortic Diseases, that man is Natzi Sakalihan. To bring us all together for the fifth time to focus on science without benefit of society dues or intrusion by infomercials is an awesome achievement, and I thank him for it.

I’ve thrown a lot of quotes at you in this little talk, but I’d like to throw out a few more, the first because it’s my favorite election year story. When Adlai Stevenson was running for president against Dwight Eisenhower, a woman called out from the audience “Senator, you have the vote of every thinking person!” Stevenson replied “That’s not enough, madam, I need a majority!” He lost to Eisenhower twice.

The last quote I offer for no other reason than that I like it. It’s from Jack Handey, and goes: “Before you criticize someone, you should walk a mile in their shoes. That way, when you criticize them, you’re a mile away and you have their shoes.” Thank you for your attention, and please enjoy this wonderful meeting.

### Conflict of Interest

The author declares no conflict of interest in regard to this publication.

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