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Perspective

Post-truth era and cardiology: After ORBITA, before CABANA

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ABSTRACT

The evidence-based medicine is rooted in the scientific truth. Oxford Dictionaries has released its 2016 word of the year: "Post-truth," which they define as "relating to or denoting circumstances in which objective facts are less influential in shaping public opinion than appeals to emotion and personal belief". In everything from climate change denial to the anti-vaccine movement, we're seeing the consequences of a failure to engage with scientific evidence. Fake news and post-truth pronouncements are increasingly common in social media and political era and are unfortunately also progressively being applied to the medical science. We also see some evidence of post-truth signals in daily cardiology procedures and guidelines including both interventional cardiology and cardiac electrophysiology. Guideline recommendations made before the randomized-controlled trials (RCT) are published might result in a scenario that the interventions or procedures have been performed on millions of people, costing billions of dollars, leading to unnecessary use of health care resources and often, ending up being even accepted as routine procedures in certain clinical situations. "Justice delayed is justice denied" is a legal cliché meaning that if timely justice is not provided to the sufferer, it loses it importance and violates human rights. In medicine, "The RCT delayed is justice denied", as highlighted by ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) trial and as may happen with CABANA (Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) in the post-truth era.

Evidence-based medicine is rooted in the scientific truth. Moreover, the trust has been considered arguably "the fundamental virtue at the heart of being a good doctor."[1] Since a fiduciary is "one who owes to another the duties of good faith, trust, confidence and candour,"[1] the doctor's relationship with the patients must be one of truthfulness. As a result, patients trust doctors to provide them with the information on which they can base a decision about whether or not to proceed with a certain procedure or treatment.[1] One possible exception might be the '*therapeutic privilege*', which refers to the withholding of information by the clinician during the consent process in the belief that disclosure of this information would lead to harm or suffering of the patient.[2]

Oxford Dictionaries has released its 2016 word of the year: "Post-truth," which they define as "relating to or denoting circumstances in which objective facts are less influential in shaping public opinion than appeals to emotion and personal belief." Rather, a post-truth society is one in which truth takes a back seat to emotion – and feelings effectively replace facts. The "post-truth" is not to be confused with "truthiness," a subtly different term that describes the phenomenon of "believing something that feels true, even if it isn't supported by facts." People have always been swayed by emotions and personal beliefs. When a fact begins to resemble whatever you feel is true, it becomes very difficult for anyone to tell the difference between facts that are true and the "facts" that are not. In everything from climate change denial to the anti-vaccine movement, we're seeing the consequences of a failure to engage with scientific evidence. Fake news and post-truth pronouncements are becoming increasingly common in social media and political era, and are unfortunately also progressively being applied to the medical sciences.[3,4] In post-truth age, the medicine exists somewhat uncomfortably in the dual world of science and belief. *Eminence based medicine* refers to a clinical decision that is made by relying purely on the opinion of a medical specialist or any prominent health professionals rather than relying on critical appraisal of scientific evidence available,[5] probably due to several reasons such as a self-serving bias or the Dunning-Kruger effect[6] or other unethical medical professionalism.[7–9] As *Abraham Maslow said* in *1966*, "If the only tool you have is a hammer, to treat everything as *if*

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it were a nail". In psychology, they call it Maslow's Hammer. As health care professionals, we should be ready to accept that our beliefs might not be more important than facts. [10] We also see some evidence of post-truth signals in daily cardiology procedures and guidelines including both interventional cardiology and cardiac electrophysiology.

Although percutaneous coronary intervention (PCI) has proven to be effective in decreasing mortality rates among patients with acute coronary syndromes (ACS), the previous meta-analyses of PCI versus optimal medical therapy for stable coronary artery disease (CAD) have not been able to demonstrate a reduction in major adverse cardiac outcomes.[11] The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[12] suggested that PCI was associated with only a modest improvement in quality of life, which actually dissipated over time. Other similar studies have consistently indicated no risk reduction in the incidence of myocardial infarction (MI) or death with PCI, except for high risk stable CAD (defined as >3% annual death or MI risk), patients with significant left main CAD, ostial left anterior descending artery disease, multivessel CAD, severe resting left ventricular dysfunction not readily explained by noncoronary causes or resting perfusion abnormalities ≥10% of the myocardium.[13] After the publication of COURAGE, the clinical guidelines emphasized medical therapy as the initial approach for management of patients with stable CAD. However, in contrast to the anticipated impact of COURAGE trial on daily practice, Garg et al. found lower rates of optimal medication use in PCI patients even after its publication.[14] The clinicians are being challenged to understand why a divergence exists between recent evidence and the conventional wisdom that PCI is associated with a large benefit in symptom relief without altering overall prognosis.[15,16] Recently, the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial has raised the bar for procedural clinical trials and has further divided the interventional cardiology community.[17] The study showed that among patients with stable angina, PCI is not associated with greater improvements in exercise times or angina frequency compared with a sham procedure, despite the presence of anatomically and functionally significant stenosis.[17] It should be noted that the ORBITA trial was an underpowered small study with short follow up (only 6 weeks) and had a low frequency of multivessel CAD; therefore, such results may not be relevant to patients with multiple lesions that are not restricted to one vessel, and should not be over-emphasized and extrapolated to patients who are more symptomatic with a more severe extent of CAD. However, this trial also does not seem to change the daily practice, even in the patient subsets for which these results are applicable. A few cardiologists discuss the evidence-based benefits of angiogram and PCI for stable CAD, and some implicitly or explicitly overstate the benefits. In some cases, experts say, doctors are motivated to use stents for financial reasons, because of the large revenue streams that stent procedures can bring to the hospitals.[18,19] In transitioning health systems, patients further develop mistrust for the physicians' motives as inequalities in health care expand and close ties between pharmaceutical companies and physicians are revealed.[20] In a study published in The Archives of Internal Medicine, Dr. Lin found that some doctors performed elective angioplasty procedures because they believed it would alleviate a patient's anxiety. Others felt that new and better stents would make a difference, or they worried that if the patient had an untoward event down the line, they would feel guilty if they did not operate.[21] In a small study in The Annals of Internal Medicine, Dr. Rothberg reported that patients with stable CAD who were told they had a blockage naturally assumed that angioplasty would be lifesaving, unless the treating doctor explained to them otherwise.[22] The National Cardiovascular Data Registry shows that at least 20% of patients who undergo elective PCI are asymptomatic.[23] The reception received by ORBITA and COURAGE trials' results further emphasizes a need for early and more number of randomized-controlled trials (RCT) prior to US Food and Drug Administration approval or international guideline recommendations[24] in order to truly understand the benefits and not cause widespread use of some procedures and management options. It has been difficult for physicians to accept the evidence that actually there is no benefit of PCI in stable CAD compared to a fake procedure[14,24] in this post-truth science era.[10,25]

We have a similar situation in cardiac electrophysiology also. Catheter ablation/isolation of pulmonary triggers has been a breakthrough innovation in the field of electrophysiology.[26] Growing experience with this technique and better atrial fibrillation (AF) suppression compared with antiarrhythmic medication have paved the way for its extended use and indication. The current AF guidelines recommend that symptom relief should be a primary goal in AF ablation and ablation should be preferred only in "highly selected" and thoroughly educated patients. Therefore, the patients' perception of their symptoms and concerns about the necessity of ablation procedures at diagnosis should be specifically addressed as part of their medical management.[27] Indeed, the main issue is that whereas AF is responsible for an increased risk of stroke and mortality, it is unclear whether patients and physicians understand that AF ablation has been shown to only improve symptomology and not reduce morbidity or mortality. [28,29] Indeed, many trials [Catheter Ablation versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction (CAMERA), Ablation versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device (AATAC) and the Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure PABA CHF)] have shown improvements in left ventricular function, exercise capacity, and quality of life after catheter ablation of AF in patients with heart failure (HF). However, the Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation (CASTLE-AF) trial was the first RCT to investigate the effect of catheter ablation on AF versus conventional first-line antiarrhythmic drug therapy on hard outcome parameters. After screening 3013 patients for eligibility, the CASTLE-AF trial, conducted with Biotronik's support, included 363 patients with symptomatic paroxysmal or persistent AF and HF with left ventricular ejection fraction (LVEF) less than 35%, and showed a 38% reduction in the composite endpoint of all-cause mortality and hospitalization for worsening HF. Since about half of the ablation patients received pulmonary vein isolation alone and the other half had pulmonary vein isolation plus additional lesions, an unexpected and interesting finding was that the maintenance of sinus rhythm was very high in the ablation arm even after 5 years, which is usually not the pattern seen in daily practice. Since the patients with an LVEF <25% showed a trend toward worse outcomes with ablation, the results should not be extrapolated to sicker, older, frailer patients (noting that most were in New York Heart Association functional class 2) and asymptomatic HF patients. Considering the fact that it took about 8 years to select 363 people among 3013 patients to enroll in the trial, if we wish to achieve similar results, we should also select the patients carefully according to strict selection criteria of the study. In an accompanying editorial, Dr Mark S Link (University of Texas Southwestern Medical Center, Dallas) noted that these findings must be interpreted conservatively given the relatively small sample size, specific criteria for patient selection, lack of blinded randomization and treatment allocation, and a complication rate that was much lower than that reported by very experienced operators in high-volume medical centers.[30] In contrast to CASTLE-AF in HF patients,

no randomized studies have been powered to demonstrate a mortality or stroke reduction benefit of rhythm control with catheter ablation over a rate control strategy in patients with normal LVEF and no signs or symptoms of HF. The only indication for AF ablation in recent guidelines has been the presence of symptoms.[31] Even though there is no scientific data about its impact on stroke or mortality, catheter ablation of AF is currently one of the most commonly performed electrophysiology procedures. The Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF)[32] trial was too small to evaluate any effect of ablation or antiarrhythmic drugs on hard outcome parameters such as stroke and/or mortality. These questions will probably remain unanswered until data from the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST) trial[33] (endpoint: composite of death, stroke, and heart failure) and the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) trial[34] (endpoint: composite of death, serious bleeding, disabling stroke, and cardiac arrest) become available. Until such time, all patients should be informed that there is no RCT showing that AF ablation lowers the risk of stroke or death. However, there is a general tendency among many proceduralists in medicine to overestimate the value and underestimate the risk of the intervention. Although the potential benefits of the procedure for asymptomatic patients are uncertain, the recent 2017 AF ablation guideline recommended that the catheter ablation could be considered in selected asymptomatic AF patients, though it was a class IIb recommendation level.[31] Although nowadays performed on a routine basis, catheter ablation of AF has the potential to cause major complications even in experienced high-volume centers. One of the most dreadful and lethal complications of AF ablation is the formation of atrioesophageal fistula (AEF). Black-Maier et al. searched the Manufacturer and User Facility Device Experience database for adverse event reports and found that the percentage of total reports involving AEF was 5.4% for CF-sensing catheters (65 of 1202) and 0.9% for non-CF-sensing catheters (13 of 1487). Overall mortality in such patients was at least 56%, with patients undergoing surgical repair more likely to survive than those treated with stenting or no intervention. Thus, AEF remains a serious complication of AF ablation despite the incorporation of protective measures and increased technical expertise[35] The question that arises is, “Do the patients know that AF itself is not necessarily a deadly heart disease while ablation might cause deadly complication such as AEF? It would not be easy to explain this complication to asymptomatic patients and hence, AF ablation should not be offered to minimally symptomatic or asymptomatic patients, even if it is labelled as a class IIb recommendation in recent guidelines[31] without RCT data. The results of ongoing CABANA and EAST trials are not expected until 2018 or 2019. In the meanwhile do we really need to be in a hurry for ablation procedure with the intention of preventing atrial structural remodeling without randomized evidence?[36] On the other side, one wonders if the results of the CABANA and EAST trials will really change the clinical practice, even if the results are negative?

We are living in the post-truth era, and the doctors have lost their trust in doctor-patients communication after loss of patient-oriented decision making.[37,38] It is important to understand how physician-patient communication has developed over time and the forces that led to these changes. The pharmaceutical and medical device companies in the past decade saw technological procedures as a major opportunity for a new and a bigger business.[7,10,39] In such an environment, propaganda-based medicine, medical commercialization, pressure through social media, and inadequate information by physicians and health care workers make it a herculean task for the patients to understand what is true and what is not.[40–42] Recent cohort studies of RCT have provided evidence of within-study selective reporting bias, where statistically significant outcomes are more likely to be more completely reported as compared to non-significant outcomes. Bias resulting from selective reporting can impact meta-analyses, influencing the conclusions of systematic reviews, and in turn, evidence based clinical practice guidelines.[43–45] One of the forgettable examples in cardiology was the removal of the Watchman LAA Closure Device in Patients With Atrial Fibrillation versus Long Term Warfarin Therapy (*PREVAIL*) *trial*[46] from the American College of Cardiology (ACC) 2013 program at the last minute because of an embargo break by the sponsor with reports of end-points being changed and attempts to not present complete data. The retraction of the Outcome of Different Ablation Strategies In Persistent and Long-Standing Persistent Atrial Fibrillation (OASIS) trial by the Journal of the American College of Cardiology also raised concerns over potential industry influence even on prominent and important scientific publications.[47] It is well recognized that pharmaceutical and medical device companies target physician ‘thought leaders’ for lucrative consulting and advisory roles.[18] Industry payments to journal editors are common and often large, particularly for certain subspecialties such as that rely on costly devices (cardiology and orthopedics) and specialties where newer drugs have recently been launched for treatment of chronic diseases (e.g. endocrinology).[18] Cardiologists, whose prescribing patterns as specialists and opinion leaders are thought to influence the prescribing patterns of non-specialists, are significantly more likely to receive direct payments from companies than are physicians in other specialties.[48] Campbell et al reported that the cardiologists were more than twice as likely as family practitioners to receive payments.[19] We need to realize that times have changed and the mutual trust between doctors and patients has been considerably eroded in this industrial-bureaucratic age of medicine.[20,28,29,37] The percentage of clinical trials conducted in academic health centers has decreased, and academic health centers are now in the minority among the locations for clinical trials.[49] Academic researchers and media have expressed concern about the influence of industry sponsorship on biomedical research, while industry is increasingly turning to private entities (such as contract research organizations) to conduct the clinical trials.[50] In addition, some clinical trials in community practices may be “seeding” trials that companies design to change prescribing habits rather than to gather scientifically useful information.[51] To restore trust, we must first acknowledge its absence in post-truth era, and then take steps to reassure patients and rebuild public trust by concentrated efforts.[20,29] Governments once again need to take a greater role in sponsoring trials for health-related problems. The practice of modern medicine is the application of science, the ideal of which has the objective of value-neutral truth. Innovations in technology have contributed to rapid changes in the way that modern medical research is carried out, and the double-blind RCTs are thought to provide optimal evidence if carried out correctly. It is clear that RCT is an experiment, but experiments may be unnecessary, inappropriate, impossible, or inadequate.[52,53] Waiting for the results of RCTs may preclude patients from an apparently-theoretically good procedure while the trials are ongoing.[54] On the other side, the best stent or innovative ablation tool or cardiac device can only bring harm to someone who doesn’t need it. However, before these RCT studies are published, the interventions evaluated in these RCT studies may already have been performed on millions of people, costing billions of dollars, leading to unnecessary use of health care resources and often, ending up being even accepted as routine procedures in certain clinical situations. It is clear that the clinical research is essential for the development of new drugs, diagnostic tests and new devices and the RCTs are thought to provide optimal evidence if carried out correctly and timely. In addition to the seeding trials, the extension of clinical indications for invasive

procedures with optimistic theory without waiting the results of "delayed" RCT is also another "hidden" problem. "Justice delayed is justice denied" is a legal cliché meaning that if timely justice is not provided to the sufferer, it loses it importance and violates human rights. In medicine, "*The RCT delayed is justice denied*" as was seen with ORBITA trial and may also happen with CABANA trial in this post-truth era.

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