What can we Learn from SOCRATES: More Questions than Answers?

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Socrates was a classical Greek scholar who had a reputation for teaching by asking questions but not necessarily providing answers. Naming a randomized trial after him is tempting fate. You might just get what you ask for – questions but no clear answers!

The SOCRATES (SOluble guanylate Cyclase stimulatoR in heArT failurE Studies) programme set out to identify one or more preferred doses of vericiguat, to take forward into major outcome trials for the treatment of recently re-compensated heart failure[1]. There were two component trials; one for left ventricular ejection fraction (LVEF) <45% (SOCRATES-REDUCED[2]) and the other for LVEF ≥45% (SOCRATES –PRESERVED[3]). The primary end-point for both was the change in amino-terminal pro-B-type natriuretic peptide (NT-proBNP); left atrial volume index was a co-primary end-point in SOCRATES-PRESERVED. Neither study met its primary endpoint. In SOCRATES-REDUCED, titration to the highest dose of vericiguat, 10mg/day, was associated with a fall in NT-proBNP, an increase in hypotensive episodes (although no difference in average blood pressure), a modest increase in LVEF and numerically fewer hospitalisations for worsening heart failure. In SOCRATES-PRESERVED, no effect on NT-proBNP or left atrial volume index was observed at any dose, there was no increase in hypotensive episodes, no obvious effect on worsening heart failure but a numerical increase in deaths with vericiguat. In one of many exploratory analyses, an improvement in quality of life was identified, largely driven by improved symptoms, amongst those titrated to the 10mg dose of vericiguat. SOCRATES-PRESERVED was marred by some errors in randomization.

Is this the correct way to phenotype heart failure? These studies used a combination of a clinical diagnosis, evidence of congestion requiring administration of diuretics, LVEF, an elevated plasma NT-proBNP and, if LVEF was >45%, left atrial dilatation to select patients

and stratify them into component trials. These are robust diagnostic criteria for heart failure but do not conform to the three LVEF phenotypes proposed by recent ESC guidelines[4]: reduced (HFrEF), mid-range (HFmrEF) and preserved (HFpEF). In clinical practice, LVEF measured by echocardiography has considerable observer variability. This was a key driver for the introduction of HFmrEF. Using a single threshold value (ie:- 40%) to distinguish HFrEF from HFpEF will misclassify many patients because of measurement error. Having HFmrEF as a grey-zone ensures that, in the future, few HFrEF patients will be misclassified as HFpEF and vice versa and that if a treatment is shown to be effective then it is clear for which phenotypes. HFmrEF may be uncommon as the first attempted clinical trial failed to enrol patients and was abandoned[5]. Pragmatically, if a treatment is shown to be effective for both HFrEF and HFpEF then it might be assumed to be effective for HFmrEF. On the other hand, a study that included both HFmrEF and HFpEF would need to show that the treatment was effective in the subgroup with HFpEF before clinicians could be sure that it was not just effective for patients with milder degrees of left ventricular systolic dysfunction, as in a recent study of spironolactone[6]. Of course, this all pre-supposes that LVEF is a useful way to phenotype heart failure. LVEF might just be a surrogate marker for other characteristics that are important determinants of outcome or treatment effect, including age, sex, the aetiology of ventricular dysfunction, the prevalence of atrial fibrillation and other co-morbidities or NT-proBNP. We should not forget that the idea of using LVEF as an entry criterion for studies of heart failure is less than 30 years old[7].

Is NT-proBNP a useful surrogate end-point for Phase II studies in heart failure? NT-proBNP is the most powerful, simple, widely available prognostic marker in patients with chronic heart failure[8]. However, plasma concentrations of natriuretic peptides in patients with **known** heart failure are not strong predictors of an adverse prognosis when measured during the

acute phase (eg:- the first 24h) of decompensated heart failure[9,10]. This may reflect a strength rather than a weakness. If a biomarker measured during the acute phase predicts longer-term prognosis then either it is a poor measure of decompensation or it is unresponsive to change and of little use in monitoring. If NT-proBNP is measured serially, then the last measured value carries most of prognostic information[11,12]. Treatments that improve prognosis, including angiotensin converting-enzyme inhibitors, mineralo-corticoid antagonists, angiotensin-receptor neprilysin inhibitors, cardiac resynchronization therapy and, more controversially, beta-blockers[13], all reduce NT-proBNP and improve prognosis. Diuretics are possibly the most effective agents for reducing NT-proBNP [14] and there is little doubt that diuretics are life-saving in severely congested patients. If NT-proBNP is a marker of congestion, a pathophysiology driven by both cardiac and renal dysfunction, and congestion is a marker of prognosis, this provides a rationale for, and limitation of, using it as a surrogate end-point in clinical trials. In decompensated heart failure, an acute intervention might temporarily relieve congestion and transiently reduce NT-proBNP. However, if the effect does not persist then an improvement in longer-term prognosis should not be expected. On the other hand, an intervention that causes a persistent reduction in NT-proBNP, should lead to improved prognosis. Whether this hypothesis is true requires the test of time and many more prospective confirmatory trials. Whether other biomarkers, such as troponin, can provide supplementary information also requires investigation.

Clearly, the published studies of vericiguat do not provide a strong argument for progressing to large outcome trials. On the other hand, they do offer some evidence of an effect. How then to proceed? The first issue is to focus on the ultimate treatment goals, which should either be important to the patient or clinician or society and preferably all three. These might include improvement (or prevention of worsening) in symptoms and well-being, reductions in

disability and morbidity, maintenance of independence or prolongation of life. Alternatively, an intervention that simplifies management and/or reduces costs might be worthwhile. The treatment goals will determine the target population and the size and duration of the next study. As most patients with heart failure are already receiving many medications, the treatment should either have a substantial benefit in order to convince physicians and patients to take an additional therapy or it needs to simplify management, for instance by making other treatments redundant. The most important therapeutic outcome will vary according to context and individual patient. For a patient with severe unremitting symptoms the most important outcome may not be survival but symptom relief. Paradoxically, it is probably the patient with heart failure who has the fewer symptoms and a better prognosis for whom longevity is the most important target. Large trials are required to demonstrate safety but unless a treatment is effective, safety is a clinically irrelevant since only effective treatments should be used.

If a treatment has a useful and consistent effect on symptoms and functional capacity then some form of cross-over trial should be considered, since using the patient as their own control greatly increases statsitical power. Such a trial should require less than one hundred patients. If it requires more, then the effect is unlikely to be of great clinical utility. Of course, enrolling the right patient is critical; you can only fix a problem if it exists. Although symptoms are often what provoke the patient to seek medical help, neither guidelines nor recent clinical trials pay great attention to improving them. Indeed, pride of place for improving symptoms is given to diuretics. This raises the question of what the comparator should be for trials investigating the effects of treatments on symptoms; should it be placebo, an increased dose of diuretic or both? This will increase the complexity of the study design but, for an effective agent, would ensure clinical relevance. Several agents have improved

symptoms of HFpEF in clinical trials and yet these have not caused guidelines to recommend their use[15]. It is important that guidelines on heart failure are not just about procrastinating death but rather provide recommendations to promote the broader well-being of patients. There is a view that for heart failure health services, unlike for many other diseases, are less welling to pay for treatments that only improve symptoms but not prognosis.

Industry is required to charge a premium price for new treatments because they have to get a return on investment within a relatively short space of time. On solution is longer patent protection on new treatments, akin to that for artists who get at least 70 years from first performance[16]. Long patents would allow companies to get a return on their investment through volume and duration of sales rather than high costs. Health systems might pay roughly the same amount but over a longer period of time. If the focus remains on reducing morbidity and mortality, then large studies will be required. Most clinical trials that have revolutionised care enrolled fewer than 3,000 patients and most were stopped early because of the size of benefit (Figure 1). With the increasing cost and complexity of delivering care, the practical clinical value of demonstrating small benefits becomes questionable and potentially unaffordable. Recently, the PARADIGM-HF study demonstrated the superiority of sacubitril-valsartan over enalapril in more than 8,000 patients but sacubitril-valsartan only received a class 1B recommendation in guidelines; to gain a Class 1A recommendation requires a confirmatory trial in a similar population, which seems unlikely to happen.

We think Socrates would have been flattered to know that his memory had been honoured by having a clinical trial named after him more than 2,000 years after his death. To quote Earl C. Kelley [17] *"We have not succeeded in answering all our problems. The answers we have found*

only serve to raise a whole set of new questions. In some ways we feel we are as confused as ever, but we believe we are confused on a higher level and about more important things."

Legend to Figure

Trial size compared to percentage reduction in all-cause mortality in landmark clinical trials of heart failure with a reduced left ventricular ejection fraction. Major trials of agents available in one or more country belonging to the European Society of Cardiology are shown.

CONSENSUS: Cooperative North Scandinavian Enalapril Survival Study

SOLVD: Studies Of Left Ventricular Dysfunction

CHARM-Reduced:- candesartan in heart failure: assessment of reduction in mortality and morbidity

ATMOSPHERE*:- Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (note that the effect on all-cause mortality was inconclusive, since the point estimate did not reach statistical significance)

CIBIS-II: Cardiac Insufficiency Bisoprolol Study-II

MERIT-HF:- Metoprolol CR/XL (Controlled Release/Extended Release) Randomized Intervention Trial in Chronic Heart Failure

COPERNICUS:- Carvedilol Prospective Randomized Cumulative Survival study

RALES:- Randomized Aldactone Evaluation Study

EMPHASIS:- Eplerenone in Mild Patients: Hospitalization and SurvIval Study in Heart Failure

COMPANION#:- Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (cardiac resynchronization therapy with defibrillator versus control arms only)

CARE-HF:- Cardiac Resynchronization — Heart Failure Study

MADIT-II:- Multicenter Automatic Defibrillator Implantation Trial-II

SCD-HeFT:- Sudden Cardiac Death in Heart Failure Trial

RAFT:- Resynchronization-Defibrillation for Ambulatory Heart - Therapy Failure Trial (RAFT)

PARADIGM-HF:- Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. Data are also shown for sacubitril – valsartan versus an imputed placebo)

SHIFT*:- Systolic Heart failure treatment with the If inhibitor ivabradine Trial (note that the effect on all-cause mortality was inconclusive, since the point estimate did not reach statistical significance)

RELAX-AHF:- RELAXin in Acute Heart Failure (note that all-cause mortality was not a pre-specified primary or secondary endpoint in this study)

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