Myocardial Dysfunction or Coronary Artery Disease as Therapeutic Targets in Heart Failure; COMPASS Directions

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Most patients with heart failure have coronary artery disease (CAD) either as a cause of left ventricular dysfunction or as a potentially important bystander. Despite a lack of evidence of benefit, highlighted in guidelines, and concerns about adverse effects on vascular, renal and respiratory function, many such patients are prescribed aspirin (1). To date, clinical trials have failed to demonstrate that any anti-thrombotic therapy is effective for patients with heart failure and CAD, although it could be argued that none was adequately powered or designed for this purpose (2, 3).

In this issue of Circulation, Branch et al show, in a subgroup analysis from the large COMPASS trial, that patients with heart failure and CAD assigned to a combination of rivaroxaban 2.5mg twice daily and aspirin 100mg once daily had fewer cardiovascular events and a lower mortality compared to those assigned only to aspirin (4). However, the recently reported COMMANDER-HF trial failed to show that adding rivaroxaban 2.5mg bd to background treatment with anti-platelet agents reduced mortality in patients with a recent hospitalisation for worsening heart failure. Can these apparently conflicting sets of data be reconciled, and should this new information alter clinical practice?

Demonstrating that an intervention directed at a therapeutic target, such as CAD, improves outcome provides insights into pathways of disease progression. Conceptually, anti-thrombotic agents are designed to reduce the rate of vascular occlusion and consequently myocardial infarction and stroke. However, myocardial occlusion may present in many ways, including sudden death, which may be vascular and/or arrhythmic, 'noisily' with chest pain and myocardial infarction or 'silently' with worsening myocardial function, heart failure or atrial fibrillation (1). Surprisingly, whether treatment directed at CAD in patients with heart failure improves outcome is in doubt. Trials of heart failure and a reduced left ventricular ejection fraction (HFrEF) have failed to demonstrate substantial overall benefit from revascularisation (5, 6), statins (7) or anti-thrombotic agents (1). On the other hand,

treatments, such as beta-blockers and antagonists of the renin-angiotensin-aldosterone system, appear similarly effective whether or not the patient has CAD. Indeed, with modern therapy, it appears that patients with HFrEF with and without CAD have a similar prognosis (8). These considerations cast doubt on the value of routine diagnostic coronary angiography for people with heart failure.

The COMPASS trial enrolled 27,395 patients with stable atherosclerotic disease, 5,902 of whom had a history of heart failure, and randomly assigned them to aspirin 100mg/day, rivaroxaban 5mg bd or rivaroxaban 2.5mg bd plus aspirin 100mg/day (4). Patients with a left ventricular ejection fraction or poorly controlled congestion with severe symptoms were excluded. The primary composite endpoint was stroke, myocardial infarction or cardiovascular death. The trial was stopped early due to a modest absolute but statistically robust benefit, one of several drawbacks of trials that are too large and consequently too short. In the overall trial, rivaroxaban 5mg bd was neither clearly superior to aspirin nor clearly inferior to combination therapy but its effect may have been underestimated due to the early termination of the trial. The benefit of combined therapy, in relative terms, was similar in patients with and without heart failure but those with heart failure were at higher risk and therefore their absolute gain was greater. Amongst patients with heart failure, the reduction in the primary endpoint and in all-cause mortality was similar with rivaroxaban, alone or in combination, compared to aspirin alone. Patients with heart failure had a smaller increase in the risk of bleeding and therefore a greater net-benefit than any other patient-subgroup. Rivaroxaban 5mg bd was associated with a slightly lower excess bleeding risk than the combination of rivaroxaban and aspirin.

Most patients had heart failure with a preserved left ventricular ejection fraction (HFpEF) and it was in this group that the benefits of combination therapy were clearest. However, substantial diagnostic misclassification is likely; only a minority of patients with heart failure

were taking diuretics, the pharmaco-epidemiological hallmark of heart failure that indicates heightened morbidity and mortality, whereas 25% of patients who were not supposed to have heart failure were taking diuretics. Unfortunately, the proportions receiving thiazide-like agents, commonly used for hypertension, or loop diuretics, usually reserved for heart failure, are not available. More attention to the detection and confirmation of heart failure; both at baseline, for subgroup analyses, and during follow-up, for outcomes might have identified an even greater benefit for patients with heart failure. A Universal Definition for Heart Failure based on measurement of natriuretic peptides should be considered routine in future trials of cardiovascular interventions (9).

Recent trials of aspirin for primary prevention have been neutral or worse, stimulating a fresh examination of aspirin's role for secondary prevention (10). It comes as a surprise to many cardiologists that there is no trial of long-term aspirin administration for patients with well-established CAD that shows a reduction in mortality (1). In the largest, long-term trial of aspirin after myocardial infarction (n = 4524; average follow-up 38 months) mortality was 10.8% amongst those assigned to aspirin compared to 9.7% of those assigned to placebo (11). The use of a large dose of aspirin (1,000mg/day) might have been responsible for the trial's neutrality, either because high doses of aspirin are less safe, less effective or less well tolerated, but excuses for failure do not constitute evidence of benefit. There is no long-term, placebo-controlled trial of aspirin after a myocardial infarction at a dose of less than 300mg/day. In the only large, randomised, placebo-controlled trial of lower doses after myocardial infarction, aspirin (160mg/day) was given for only 28 days and then stopped; treatment differences were still apparent a decade later (1). Perhaps aspirin should be given as a short course after an acute vascular event rather like an antibiotic for pneumonia? The current popularity of aspirin owes more to publication bias, over-reliance on meta-analysis and the popular press than to robust scientific evidence. The lack of evidence of efficacy or

safety of aspirin in patients with CAD and heart failure frustrates robust interpretation of the COMPASS trial.

The COMMANDER-HF trial enrolled patients exclusively with HFrEF, who had recently been discharged after a hospitalisation for worsening heart failure and randomly assigned them to placebo or rivaroxaban 2.5mg twice daily in addition to background antiplatelet therapy, generally low-dose aspirin but about one third were also taking clopidogrel. Many patients admitted with worsening heart failure were ineligible for the trial because they were in atrial fibrillation and required full anti-coagulation. The trial was neutral on its composite primary endpoint of all-cause mortality, myocardial infarction and stroke but a post-hoc analysis suggested a reduction in vascular events; a composite of sudden death, myocardial infarction and stroke(12). The reduction in stroke in COMPASS (42%) and COMMANDER-HF (34%) was similar and nominally significant in both trials.

Taken together, these trials suggest that patients with CAD and heart failure benefit from rivaroxaban provided congestion is controlled and they do not have a severely reduced left ventricular ejection fraction. The data are strongest for HFpEF. However, for those with more severe symptoms or ventricular dilatation, the key drivers of outcome appear to be myocardial dysfunction and congestion rather than vascular or arrhythmic events (Figure). Similarly, for patients with well controlled congestion, implantable cardioverter defibrillators reduce rates of sudden death and meaningfully prolong life but are ineffective for those with more severe congestion (13). Patients with advanced heart failure may be unlikely to survive a serious vascular or arrhythmic event, but may still benefit from treatments that improve myocardial function, remodelling and congestion.

In conclusion, the severity of heart failure should influence the choice of therapy. Cardiovascular interventions are likely to be most beneficial for those who are neither so well

that treatment is unnecessary nor so sick that they cannot respond (14). Treatments for CAD, including 'low-dose' rivaroxaban and statins, appear similarly beneficial for patients with and without heart failure providing congestion is well controlled and left ventricular dilatation is not severe but for patients with poorly controlled congestion, treatments directed at vascular or arrhythmic events are likely to fail. However, controlling congestion might allow patients to regain the benefits of treatments for CAD. Unfortunately, the COMPASS trial was not designed to provide evidence for the safety and efficacy of aspirin in heart failure. The trial shows that rivaroxaban 5mg bd alone is not inferior to combined therapy with aspirin and rivaroxaban 2.5mg bd and might be associated with a lower bleeding risk. Accordingly, a low dose of rivaroxaban could be considered the current anti-thrombotic treatment of choice for patients with CAD and heart failure with well-controlled congestion. Whether the dose of rivaroxaban should be 2.5mg bd or 5mg bd depends on whether aspirin is, in your opinion, effective; recognising that such an opinion is unsupported by any facts.

Legend to Figure:-

Concept figure showing possible scenarios of absolute (AC) and relative (RC) contributions of different types of events occurring over two years according to New York Heart Association (NYHA) functional classification of the symptomatic severity of heart failure. For instance, for patients in NYHA Class 0/1, 4% (AC) of deaths are expected to be non-cardiovascular (non-CVD) and this will constitute 33% (RC) of all-events for this class. For patients in NYHA class 0/1, non-fatal vascular events (NFVE) and sudden vascular death (SVD) combined make an AC of 6% and RC of 49% to the total number of events (death or NFVE) over a two-year period. For patients in NYHA Class 4, SVD and NFVE combined also make an AC of 6%. Although the absolute rate of vascular events does not change with

increasing severity of heart failure, the presentation changes from predominantly non-fatal to predominantly fatal. However, the RC of SVD and NFVE to all events is only 12% because myocardial dysfunction, leading to death from worsening congestion or terminal arrhythmias, is driving prognosis. Note that these numbers reflect expert opinion rather than being derived from original data and are for illustrative purposes only.

Reference List

1. Cleland JGF. Physicians Addicted to Prescribing Aspirin-a Disorder Of Cardiologists (PAPA-DOC) Syndrome: The Headache of Nonevidence-Based Medicine for Ischemic Heart Disease? *JACC Heart Fail* 2018;**6**(2):168-171.

2. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *AM HEART J* 2004;**148**(1):157-164.

3. Homma S, Thompson JL, Sanford AR, Mann DL, Sacco RL, Levin B, Pullicino PM, Freudenberger RS, Teerlink JR, Graham S, Mohr JP, Massie BM, Labovitz AJ, Di Tullio MR, Gabriel AP, Lip GY, Estol CJ, Lok DJ, Ponikowski P, Anker SD. Benefit of warfarin compared with aspirin in patients with heart failure in sinus rhythm: a subgroup analysis of WARCEF, a randomized controlled trial. *Circ Heart Fail* 2013;**6**(5):988-997.

4. Branch KR, Probstfield JL, Eikelboom JW, Bosch J, Maggioni AP, Cheng RK, Bhatt DL, Avezum A, Fox KAA, Connolly SJ, Shestakovska O, Yusuf S. Rivaroxaban With or Without Aspirin in Patients with Heart Failure and Chronic Coronary or Peripheral Artery Disease: The COMPASS Trial. *Circulation* 2019.

5. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL. Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction. *N Engl J Med* 2011.

6. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, Chattopadhyay S, Norell MS, Pennell DJ, Senior R. The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail* 2011;**13**(2):227-233.

7. Cleland JG, McMurray JJ, Kjekshus J, Cornel JH, Dunselman P, Fonseca C, Hjalmarson A, Korewicki J, Lindberg M, Ranjith N, Van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). *J AM COLL CARDIOL* 2009;**54**(20):1850-1859.

8. Udelson JE. Is Heart Failure Etiology Destiny?: Outcome and Therapeutic Implications. *JACC Heart Fail* 2019;**7**(6):466-468.

9. Cleland JGF, Pellicori P, Clark AL. Prevention or Procrastination for Heart Failure?: Why We Need a Universal Definition of Heart Failure. *J Am Coll Cardiol* 2019;**73**(19):2398-2400.

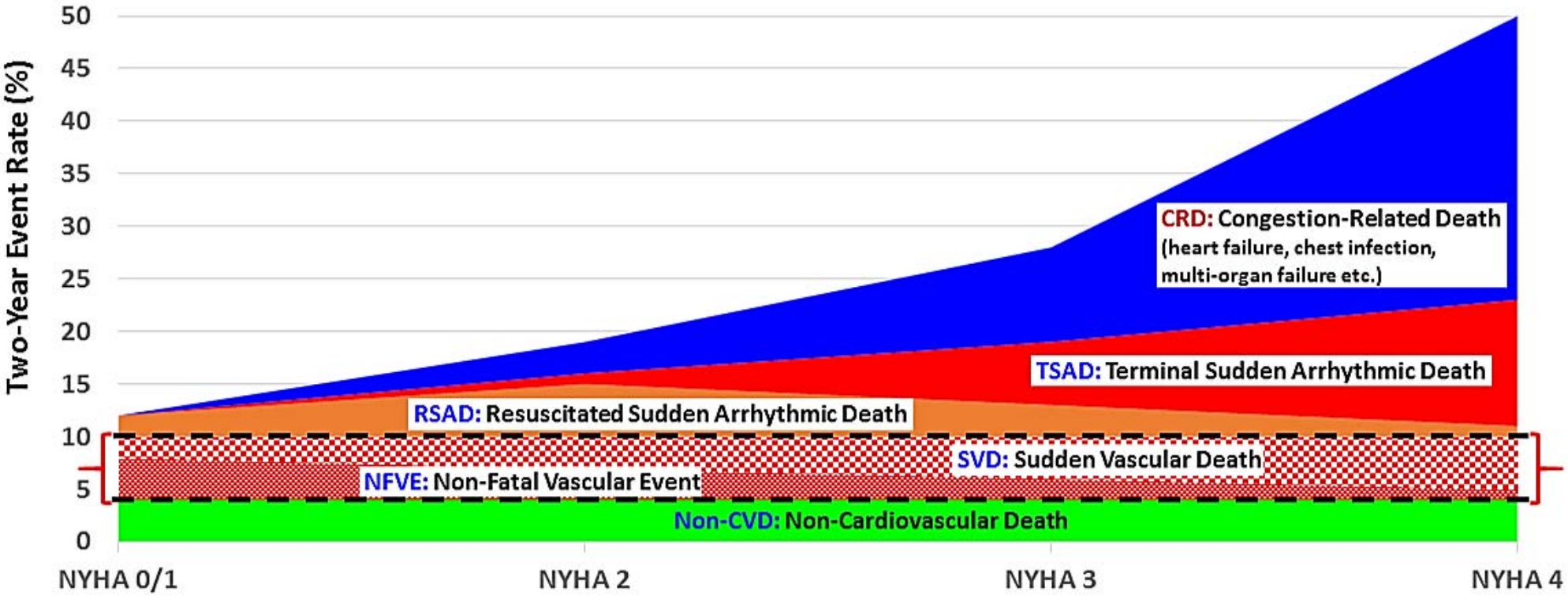
10. Raber I, McCarthy CP, Vaduganathan M, et al. The rise and fall of aspirin in the primary prevention of cardiovascular disease. *Lancet* 2019;**393**:2155-2167.

11. Aspirin Myocardial Infarction Study Research Group. A randomised, controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980;**243**:661-668.

12. Greenberg B, Neaton JD, Anker SD, Byra WM, Cleland JGF, Deng H, Fu M, La Police DA, Lam CSP, Mehra MR, Nessel CC, Spiro TE, Van Veldhuisen DJ, Vanden Boom CM, Zannad F. Association of Rivaroxaban With Thromboembolic Events in Patients With Heart Failure, Coronary Disease, and Sinus Rhythm: A Post Hoc Analysis of the COMMANDER HF Trial. *JAMA Cardiol* 2019.

13. Cleland JG, Hindricks G, Petrie MC. The shocking lack of evidence for implantable cardioverter defibrillators for heart failure; with or without cardiac resynchronization. *Eur Heart J* 2019.

14. Cleland JG, Tavazzi L, Daubert J-C, Tageldien A, Freemantle N. Cardiac Resynchronization Therapy. Are Modern Myths Preventing Appropriate Use? *J Am Coll Cardiol* 2009;**53**(7):608-611.



	NYHA 0/1		NYHA 2		NYHA 3		NYHA 4	
Reduction →	*Absolute*	*Relative*	*Absolute*	*Relative*	*Absolute*	*Relative*	*Absolute*	*Relative*
CRD	0%	0%	3%	16%	9%	32%	27%	54%
TSAD	0.2%	2%	0.5%	3%	6%	21%	12%	24%
RSAD	2%	16%	5%	27%	3%	11%	1%	2%
SVD	2%	AC / RC 6% / 49% 16%	3%	AC / RC 6% / 32% 16%	4%	AC / RC 6% / 21% 14%	5%	AC / RC 6% / 12% 10%
NFVE	4%	33%	3%	16%	2%	7%	1%	2%
Non-CVD	4%	33%	4%	22%	4%	14%	4%	8%