Table 1
Patient and joint associations of socioeconomic status and cardiorespiratory fitness with risk of sudden cardiac death

Socioeconomic status (SES)	Events/Total (268/2368)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
High SES	81/961	1 (reference)	1 (reference)
Moderate SES	75/569	1.34 (0.97-1.85)	1.32 (0.95-1.82)
Low SES	112/838	1.38 (1.02-1.87)	1.33 (0.98-1.80)
Cardiorespiratory fitness (CRF)			
Low	132/782	1 (reference)	1 (reference)
Moderate	78/774	0.70 (0.52-0.95)	0.72 (0.53-0.98)
High	58/812	0.64 (0.45-0.93)	0.66 (0.46-0.95)
Combined SES and CRF		*Adjusted HR (95% CI)	
High SES / Fit	42/710	1 (reference)	
Low SES / Fit	46/484	1.41 (0.92-2.16)	
High SES / Unfit	85/624	1.57 (1.06-2.34)	
Low SES / Unfit	95/550	2.04 (1.37-3.02)	

CI= confidence interval; CRF= cardiorespiratory fitness; HR= hazard ratio; SES= socioeconomic status
Model 1: Adjusted for age, smoking, alcohol consumption, body mass index, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, diabetes, anti-hypertensive medication, family history of coronary heart disease, history of cardiovascular disease, and physical activity. Model 2: adjusted for model 1 plus CRF when SES is exposure or SES when CRF is exposure.

that CRF attenuated the incidence of SCD in men with low SES highlight that importance of enhancing physical activity levels due to its widespread benefits and inherently inexpensive nature as a strategy for lowering the incidence of SCD, thereby improving survival outcomes in underserved populations.[1]

There is a methodologic limitation to be acknowledged in this prospective study. First, this prospective study included only middle-aged Caucasian men, thus limiting the generalizability of our findings to women, other race and/or ethnicity, and age groups. Nevertheless, the strength of this prospective study was the use of directly measured peak oxygen consumption using metabolic gas analysis, which provides an objective and quantitative measure of CRF.

In conclusion, SES and CRF are independently associated with the incidence of SCD and that high levels of CRF modifies the association between SES and the incidence of SCD in the general population.

Disclosures

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1. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, Quyyumi AA, Taylor HA, Gulati M, Harold JG, Mieres JH, Ferdinand KC, Mensah GA, Sperling LS. Socioeconomic Status and cardiovascular outcomes: challenges and interventions. *Circulation* 2018;137:2166–2178.
2. Reinier K, Thomas E, Andrusiek DL, Aufderheide TP, Brooks SC, Callaway CW, Pepe PE, Rea TD, Schmicker RH, Vaillancourt C, Chugh SS, Resuscitation Outcomes Consortium Investigators. Socioeconomic status and incidence of sudden cardiac arrest. *CMAJ* 2011;183:1705–1712.
3. Franklin BA, Kokkinos P, Lavie CJ. Do not forget physical activity and cardiorespiratory fitness. *Am J Cardiol* 2018;122:1797–1799.
4. Jiménez-Pavón D, Lavie CJ, Blair SN. The role of cardiorespiratory fitness on the risk of sudden cardiac death at the population level: a systematic review and meta-analysis of the available evidence. *Prog Cardiovasc* 2019;62:279–287.
5. Jae SY, Kurl S, Bunsawat K, Franklin BA, Choo J, Kunutsor SK, Kauhanen J, Laukkanen JA. Impact of cardiorespiratory fitness on survival in men with low socioeconomic status. *Eur J Prev Cardiol* 2020;3. 2047487319901057.
6. Rawal LB, Smith BJ, Quach H, Renato AMN. Physical activity among adults with low socioeconomic status living in industrialized countries: a meta-ethnographic approach to understanding socioecological complexities. *J Environ Public Health* 2020;2020:4283027. https://doi.org/10.1155/2020/4283027.

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Meta-Analysis of Efficacy of Sacubitril/Valsartan in Heart Failure With Preserved Ejection Fraction

Randomized controlled trials (RCTs) of sacubitril/valsartan have suggested possible clinical benefit among patients with heart failure with preserved ejection fraction (HFpEF). The phase II PARAMOUNT (Prospective comparison of ARNI with ARB [angiotensin-receptor blockers] on Management Of HFpEF) trial found sacubitril/valsartan to significantly reduce natriuretic peptide concentrations and left atrial size, compared with valsartan.[1] In the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in HFpEF) trial, although sacubitril/valsartan did not meet the primary endpoint of a statistically significant reduction in total HF hospitalizations or cardiovascular death, the p-value was marginal and results trended towards benefit.[2] Most recently, in the PARALLAX-HF (A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients; NCT03066804) trial,[3] compared with

individualized medical therapy (predominantly valsartan and enalapril), sacubitril/valsartan met the co-primary endpoint of reduction in natriuretic peptide concentration without a benefit on other primary or secondary outcomes. However, post hoc analyses of PARALLAX-HF suggested potential improvement in clinical outcomes. In the context of mixed clinical trial results, the goal of the present meta-analysis was to combine data from existing RCTs to derive a more reliable estimate of the potential benefit of sacubitril/valsartan in HFpEF.

Medline, Cochrane library, and major scientific conferences were searched from inception until September 6th, 2020. Inclusion criteria were: (1) RCTs including use of sacubitril/valsartan as a study treatment arm; (2) population of HFpEF; and (3) reporting outcomes of interest. Outcomes of interest were change in N-terminal pro−B-type natriuretic peptide (NT-proBNP) concentration, change in the Kansas City Cardiomyopathy Questionnaire Clinical Sumary Score (KCCQ-CSS) score, ≥5-point improvement in KCCQ-CSS, change in the New York Heart Association (NYHA) functional class, hospitalization for heart failure (HHF) (assessed as time to first event), and all-cause mortality. The inverse variance of the mean ratio and associated 95% confidence intervals (CIs) were used to assess for change in NT-proBNP. The inverse variance of weighted mean difference and associated 95% CIs were used to assess change in KCCQ-CSS. Odds ratios (ORs) and the associated 95% CIs were used to assess ≥5-point improvement in KCCQ-CSS and improvement in NYHA class. Hazard ratios (HRs) and associated 95% CIs were used to assess HHF and all-cause mortality. A random-effect model was utilized. Heterogeneity was assessed using Cochrane Q statistic, and Higgins and Thompsons' I^2. The certainty of the evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and

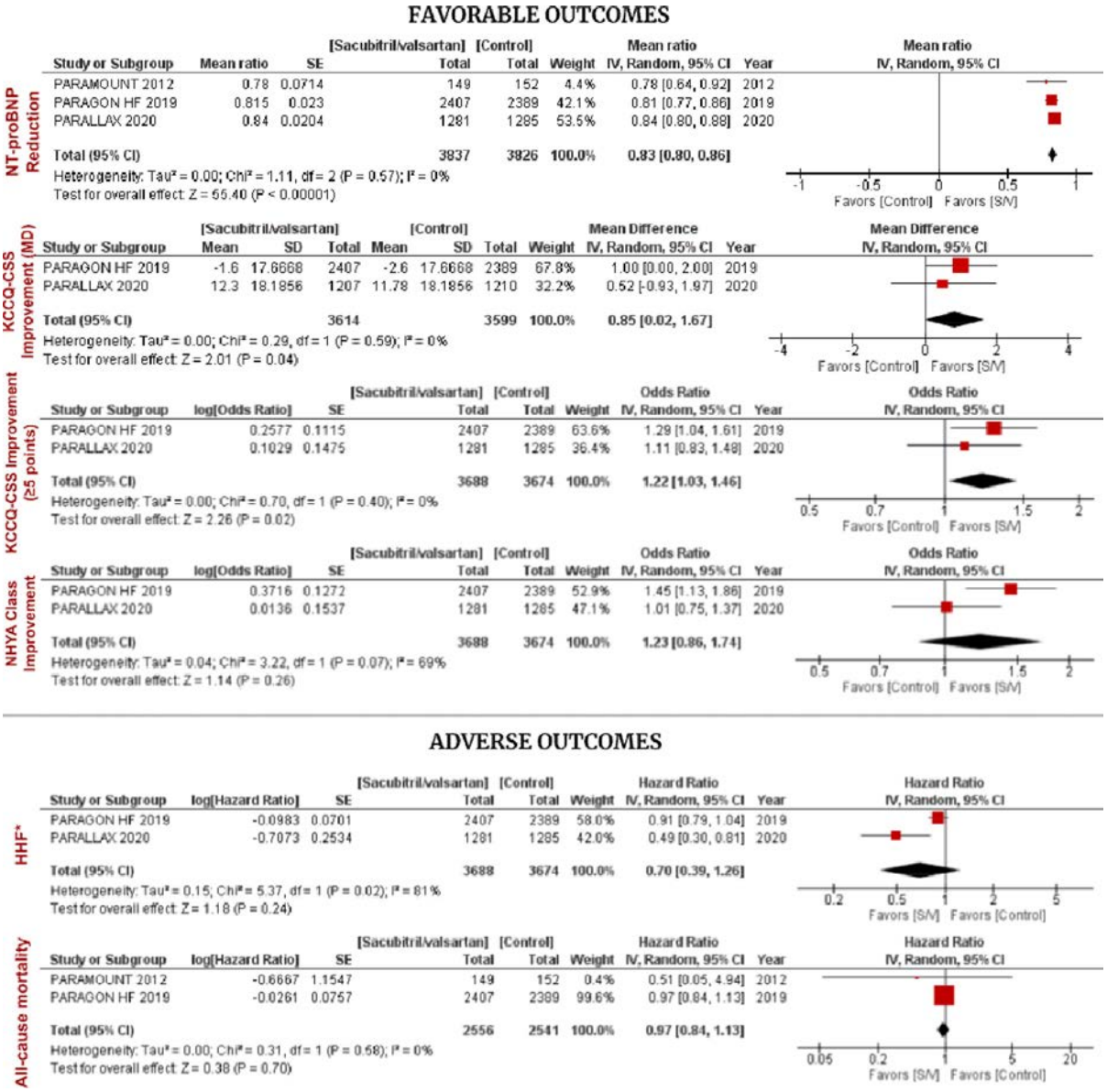

Figure 1. Forest plots examining outcomes of interest. Data for NT-proBNP reduction in PARAGON-HF abstracted from Cunningham JW et al.[5] Data for time-to-first HHF in PARAGON-HF abstracted from Solomon SD et al.[6] KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; HHF = hospitalization for heart failure; NYHA = New York Heart Association; MD = mean difference; NT-proBNP = N-terminal pro−B-type natriuretic peptide; S/V = sacubitril/valsartan. *HHF results from the PARALLAX trial from post hoc analysis of events that were documented as adverse events and were not adjudicated.

Evaluation) approach. Assessment of publication bias was not done due to low number of studies (<10).

Three RCTs with 7669 total patients met criteria for inclusion.[1,2,4–6] Overall, 3,837 (50%) patients received sacubitril/valsartan. Compared with control, sacubitril/valsartan led to incremental reduction in NT-proBNP concentration (mean ratio 0.83; 95% CI [0.80,0.86]; $I^2 = 0\%$; certainty: high), improvement in KCCQ-CSS score (mean difference +0.85; 95% CI [0.02,1.67]; $I^2 = 0\%$: certainty: high), and greater likelihood of ≥5-point improvement in KCCQ-CSS (OR 1.22; 95% CI [1.03,1.46]; $I^2 = 0\%$: certainty: high). There was no significant effect on change in NYHA functional class (OR 1.23; 95% CI [0.86,1.74]; $I^2 = 69\%$: certainty: moderate). Sacubitril/valsartan did use not significantly decrease the risk of HHF (HR 0.70; 95% CI [0.39,1.26]; $I^2 = 81\%$: certainty: moderate) or all-cause mortality (HR 0.97; 95% CI [0.84,1.13]; $I^2 = 0\%$: certainty: low) (Figure 1).

This meta-analysis suggests incremental benefit with sacubitril/valsartan for patients with HFpEF. These benefits were primarily limited to reductions in NT-proBNP and improvements in patient-reported quality of life. Limitations of this meta-analysis should be noted. First, data from PARALLAX-HF were presented at the 2020 European Society of Cardiology Congress but are not published. Second, trials had variable follow-up periods for outcome assessment. Third, definitions of HFpEF and eligibility criteria varied slightly between trials. Lastly, while the PARAMOUNT and PARAGON-HF trials used valsartan as control, the PARALLAX-HF trial compared individualized medical therapy, which included valsartan, enalapril, or placebo. Nonetheless, >87% of patients in PARALLAX were randomized with an active control of valsartan or enalapril.

Although there is no established therapy for HFpEF, many HFpEF patients in clinical practice receive renin-angiotensin system inhibitors (RASi) for management of comorbidities (e.g., hypertension, chronic kidney disease). This meta-analysis suggests that compared with conventional RASi, sacubitril/valsartan is non-inferior across endpoints tested, and superior for NT-proBNP and quality of life. Thus, for HFpEF patients in whom RASi therapy is otherwise indicated, use of sacubitril/valsartan may be reasonable. Further randomized clinical trials are needed to clearly define the role of sacubitril/valsartan in HFpEF and subsets of patients who may benefit most. The PARAGLIDE-HF (NCT03988634) trial will study the efficacy and safety of sacubitril/valsartan among patients hospitalized and recently hospitalized with HFpEF.

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17 January 2021

1. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJV. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;380:1387–1395.
2. Solomon SD, McMurray JJ V, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen H, Goncalvesova E, Katova T, Saraiva JFK, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019;381:1609–1620.
3. Wachter R, Shah SJ, Cowie MR, Szecsödy P, Shi V, Ibram G, Zhao Z, Gong J, Klebs S, Pieske B. Angiotensin receptor neprilysin inhibition versus individualized RAAS blockade: design and rationale of the PARALLAX trial. *ESC Heart Fail* 2020;7:856–864.
4. Pieske B, Shah SJ, Wachter R, Solomon SD, Szecsoedy P, Ibram G, Shi V, Zhao Z, Cowie M. Angiotensin receptor neprilysin inhibition compared with individualized medical therapy for comorbidities in patients with heart failure and preserved ejection fraction – the PARALLAX trial. In: Hot Line Session at the European Society of Cardiology Congress; 2020.
5. Cunningham JW, Vaduganathan M, Claggett BL, Zile MR, Anand IS, Packer M, Zannad F, Lam CSP, Janssens S, Jhund PS, Kober L, Rouleau J, Shah SJ, Chopra VK, Shi VC, Lefkowitz MP, Prescott MF, Pfeffer MA, McMurray JJ, Solomon SD. Effects of sacubitril/valsartan on n-terminal pro-b-type natriuretic peptide in heart failure with preserved ejection fraction. *JACC Heart Fail* 2020;8:372–381. https://doi.org/10.1016/j.jchf.2020.03.002.
6. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, Rouleau J, Pfeffer MA, Desai A, Lund LH, Kober L, Anand I, Sweitzer N, Linssen G, Merkely B,

Arango JL, Vinereanu D, Chen C, Senni M, Sibulo A, Boytsov S, Shi V, Rizkala A, Lefkowitz M, McMurray JJ. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation* 2020;141:352–361.

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Coronary Sinus Reducers and Internal Mammary Artery Occlusion: Giambattista Vico's Recurring Cycles Within the History of Civilization

With great interest, I read the article by D'Amico et al[1] reporting on the usefulness of a coronary sinus (CS) reducer, a percutaneous endo-luminal stent, for treating refractory angina. The principle behind implanting this device is focal narrowing in the lumen of the CS, which activates a short cascade of events. First, it creates a pressure gradient across the device, including an increase in backward pressure in venules and capillaries. Secondly, it causes microvascular blood redistribution from the less ischemic sub-epicardium to more ischemic endocardium, thereby adjusting the normal blood flow ratio between the heart's layers. Thirdly, it reduces myocardial ischemia and angina. Encouraging empirical results moved the European Society of Cardiology to include this technique in their 2019 guidelines as a valuable treatment for refractory angina, calling it a class IIb recommendation based upon B-level evidence.[2]

Exactly one century ago, Louis Gross demonstrated that the human heart could benefit from three vascular mechanisms to compensate for myocardial ischemia.[3] The most important of these is the widening of intra-myocardial anastomotic channels, especially within the ventricular septum. The second is the development of the *rami telae adiposae*, a microvascular network located in the epicardial mantle bi-directionally connecting to myocardial small vessels and the periaortic and peri-pulmonic vasa vasorum. The third mechanism consisted of connections between small myocardial vessels and extra-cardiac arteries, like the bronchial, intercostal, oesophageal, pericardial and, above all, internal mammary arteries (IMAs), a network that, later in the seventies, was named "noncoronary collateral myocardial blood flow" (or "noncoronary collateral circulation") by cardiac surgeon Gerald Buckberg.[4] Beside these observations, Gross also introduced the principle of CS occlusion, his experiments on canine models, conducted in the thirties, revealing that partial occlusion of the CS (more than complete occlusion) was protective against the ischemic effects of proximal left anterior descending artery ligation.[5] Among 29 dogs on which he tested his theory, 20 survived one to three weeks; and, in more than 50%, the infarct area either was smaller than in control dogs, or absent altogether. Based on the same principle, Mercier Fauteux, in Montreal, ligated the great cardiac vein in dogs in 1935, and performed the first operation in man in 1939, the patient remaining free from angina at two-year follow up.[6] Further operations on subsequent patients followed.

Over the same decade, Davide Fieschi, in Italy, invented the technique of IMA surgical ligation distal to the origin of the pericardiophrenic branch, achieved through a small incision within the 4th or 5th intercostal space.[7] Occlusion of the IMAs had the goal of redirecting blood flow to the heart via these branches. This technique was used successfully by Battezzati in 304 patients and by other groups in the fifties.[7] Although some continued to advocate for its use, this approach ultimately was abandoned after the cardiopulmonary bypass machine was invented and coronary surgery expanded, giving pause to further debate.

Since 2010, after 50 years of obscurity, the principle of IMA occlusion has been resurrected by the current author as a possible tool for treating refractory angina.[8,9] These arteries certainly have high plastic potential in developing collaterals.[10-16] Endovascular embolization or occlusion of the IMAs, using plugs, was suggested, considering also that the theoretical risk of such a procedure is very low, similar to that of simple coronary angiography.[17,18] Over the last eight years, a group of interventional cardiologists in Bern has iteratively demonstrated that, in man, transient or permanent occlusion of the IMAs, distal to the origin of the peri-cardio-phrenic branch, increases the collateral flow index and fractional flow reserve, while decreasing anginal symptoms and ST anomalies on intracoronary electrocardiograms (ECGs).[19,20] They have concluded that permanent IMA occlusion augments extracardiac ipsilateral coronary supply, with the effect of reducing ischemia in the dependent myocardial region. This conclusion is astonishingly in agreement with that of our Italian precursors. Albeit not yet accepted as an established therapeutic option, this method could theoretically become an alternative to CS reducer use, or at least a complementary tool, if both are used in the same patient, certainly warranting further investigation.

As expressed above, CS reducers and IMA occlusion both are principles based upon old concepts, abandoned for decades, but recently resurrected. The famous philosopher Giambattista Vico (Naples, 1668 to 1744) theorized that the history of civilization consists of "corsi e ricorsi storici".[21] In English, this usually is translated as "occurrences and recurrences of history" or as "recurring cycles within the history of civilization." The reappearance and reapplication of old concepts in clinical practice suggests that medicine too is prone to evolutionary and cyclical changes,[22,23] with cardiology no exception.

DECLARATION OF INTERESTS

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1. D'Amico G, Giannini F, Massussi M, Tebaldi M, Cafaro A, Ielasi A, Sgura F, De Marco F, Stefanini GG, Ciardetti M, Versaci F, Latini RA, Saccà S, Ghiringhelli S, Picchi A, Cerrito M, Gaspardone A, Tarantini G. Usefulness of coronary sinus reducer implantation for the treatment of chronic refractory angina pectoris. *Am J Cardiol* 2021;139:22–27. https://doi.org/10.1016/j.amjcard.2020.09.045. Epub 2020 Sep 28. PMID: 32998007.
2. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–