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Published in:
Circulation

DOI:
10.1161/CIRCULATIONAHA.121.057429

Publication date:
2022

Circulation

RESEARCH LETTER

Impact of Sacubitril/Valsartan Versus Ramipril on Total Heart Failure Events in the PARADISE-MI Trial

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The hypothesis that sacubitril/valsartan is superior to ramipril in reducing time-to-first cardiovascular death or the development of heart failure (hospitalization or outpatient) in patients with acute myocardial infarction was tested in PARADISE-MI (Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after MI).[1] The risk of this primary composite outcome using the prespecified time-to-first event analysis of the clinical end point committee (CEC)–adjudicated events was not significantly reduced in the sacubitril/valsartan group.[2] As such, all secondary analyses are considered exploratory.

Because the comparator arm renin-angiotensin system inhibitor has previously proven effective in reducing mortality in this population, exploring additional prespecified end points could offer relevant information regarding the effects of angiotensin receptor neprilysin inhibition in high-risk patients after myocardial infarction. This research letter provides analyses regarding more expansive evaluations of clinical outcomes focusing on total (first and recurrent) CEC-adjudicated, and investigator-reported events, as well.

METHODS

The design, baseline characteristics, and primary results of this institutional review board–approved trial are published.[1,2] In brief, PARADISE-MI was a double-blind, active-controlled randomized, clinical trial that compared sacubitril/valsartan with ramipril in 5661 patients with written informed consent, an acute myocardial infarction (within 0.5–7 days of presentation) with either left ventricular ejection fraction ≤40% or transient pulmonary congestion. Previous heart failure or clinical instability (requiring intravenous diuretics, inotropes, or blood pressure support within the 24 hours before randomization) were major exclusions, and all patients provided written informed consent.

Time-to-first event data were analyzed using Cox models, whereas timing and occurrence of recurrent events (hospitalizations for heart failure, outpatient heart failure, or cardiovascular death) were analyzed using a negative binominal regression model with a Weibull baseline intensity function with treatment, type of myocardial infarction, percutaneous coronary intervention, and region as factors.[2] Analyses are exploratory and *P* values were not adjusted for multiplicity. Data are available on request from the authors.

RESULTS

In the previously reported time-to-first analysis of CEC-adjudicated primary events, there were 338 patients (11.9%) with a first event among the 2830 randomly assigned to sacubitril/valsartan and 373 patients (13.2%) with a first event among the 2831 randomly assigned to ramipril (hazard ratio, 0.90 [95% CI, 0.78–1.04], *P*=0.17).[2] Comparisons between the components of the end points were previously reported.[2]

Key Words: heart failure ■ myocardial infarction ■ ramipril ■ sacubitril/valsartan

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This manuscript was sent to Faiez Zannad, Guest Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 89.

Circulation is available at www.ahajournals.org/journal/circ

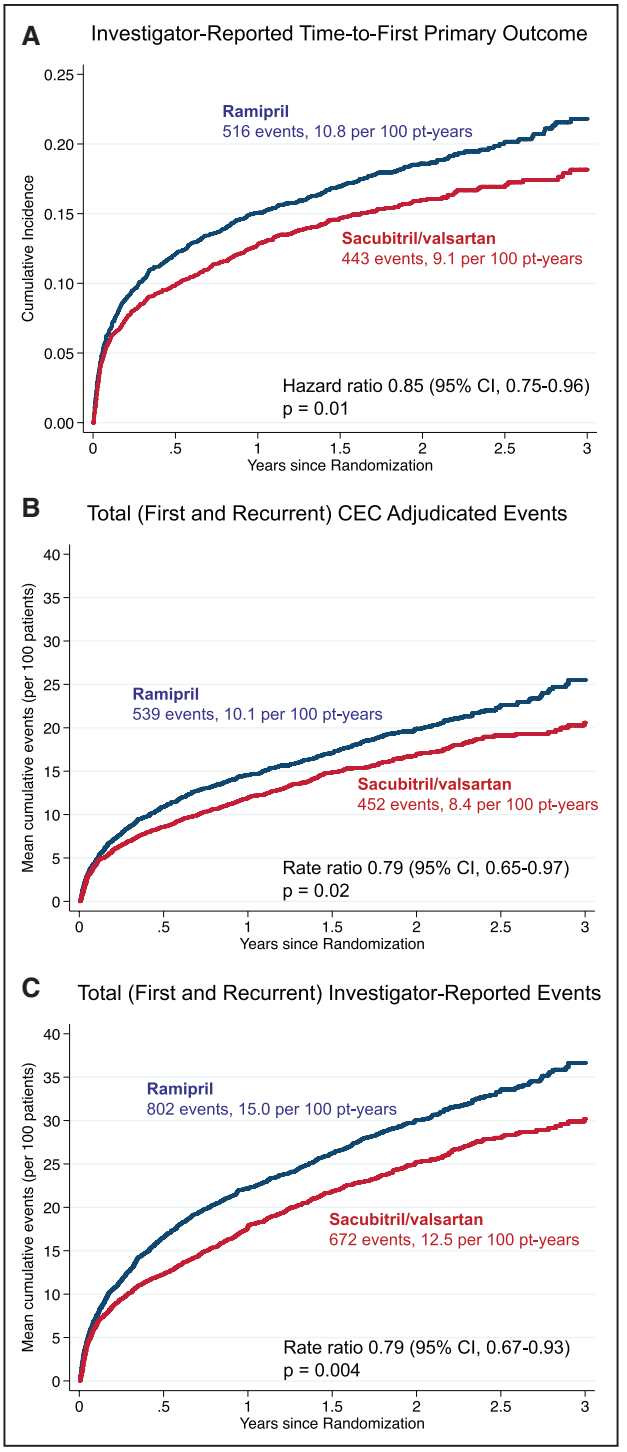

Figure. Clinical outcomes.
Shown are Kaplan-Meier curves for the investigator-reported primary composite outcome, analyzed as time to first event (**A**), and Nelson-Aalen event curves for total (first and recurrent) clinical end point committee (CEC)–adjudicated (**B**) and investigator-reported (**C**) primary events of total hospitalizations for heart failure, total outpatient episodes of symptomatic heart failure, and cardiovascular death. **A**, Investigator-reported time-to-first event: 443 patients (15.7%) in the sacubitril/valsartan group (cardiovascular death, 115; hospitalization, 231; and outpatient, 97) and 516 patients (18.2%) in the ramipril group (cardiovascular death, 111; hospitalization, 264; and outpatient, 141). **B**, CEC adjudicated total primary events: (*Continued*)

Investigator-Reported Time-to-First Event

Among the patients randomly assigned to sacubitril/valsartan, there were 443 patients (15.7%) with a first investigator-reported cardiovascular death, hospitalization for heart failure, or outpatient heart failure, and among the patients randomly assigned to ramipril there were 516 patients (18.2%) with one of these events (hazard ratio, 0.85 [95% CI, 0.75–0.96], *P*=0.01; Figure [A]).

CEC-Adjudicated Total (First and Recurrent) Events

In the sacubitril/valsartan group, there were a total of 452 CEC-adjudicated primary events among 338 patients with at least one of these events, whereas there were 539 total events among 373 patients in the ramipril group (rate ratio, 0.79 [95% CI, 0.65–0.97], *P*=0.02; Figure [B]). The use of open label sacubitril/valsartan after a CEC-confirmed heart failure event (hospitalization or outpatient episode) was 17 of 199 (8.5%) in the sacubitril/valsartan group and 16 of 234 (6.8%) in the ramipril group.

Investigator-Reported Total (First and Recurrent) Events

In the sacubitril/valsartan group, there were 672 investigator-reported total events among 443 patients with at least one of these events, whereas in the ramipril group, there were 802 total events among 516 patients (rate ratio, 0.79 [95% CI, 0.67–0.93], *P*=0.004; Figure [C]). The use of open label sacubitril/valsartan following an investigator report of heart failure was 23 of 327 (7.0%) in the sacubitril/valsartan group and 28 of 400 (7.0%) in the ramipril group.

DISCUSSION

When the results of a major randomized trial fail to achieve the level of significance to declare a difference for its primary objective, additional analyses may provide useful information. Questions have been proposed to better understand, although not to change, the neutral result.[3] With adequate statistical power and no major deficiencies in trial design or conduct, this retrospective probing of PARADISE-MI focused on choice of the primary outcome. Although recurrent event analyses cap-

Figure Continued. 452 primary events in the sacubitril/valsartan group (240 hospitalizations, 44 outpatient episodes, and 168 cardiovascular deaths) and 539 events in the ramipril group (286 hospitalizations, 62 outpatient episodes, and 191 cardiovascular deaths). **C**, Investigator-reported total primary events: 672 primary events in the sacubitril/valsartan group (395 hospitalizations, 122 outpatient episodes, and 155 cardiovascular deaths) and 802 events in the ramipril group (447 hospitalizations, 176 outpatient episodes, and 179 cardiovascular deaths).

ture a more complete assessment of the adverse patient and economic impact of heart failure, time-to-first event analysis was chosen because once a patient in PARADISE-MI developed heart failure, open label sacubitril/valsartan use was anticipated to confound the recurrent event analysis. In retrospect, with the minimal use of open label sacubitril/valsartan (<10%) in patients developing symptomatic heart failure during the conduct of our trial, adopting the more expansive outcome of total events would have been a more appropriate primary end point to assess the influence of sacubitril/valsartan relative to ramipril on the full burden of heart failure.

Although these exploratory analyses do not alter the primary neutral findings for use after acute myocardial infarction, the consistent findings of reductions in recurrent heart failure events using both CEC adjudications and investigator reports provides more supportive information for the already indicated replacement of an angiotensin-converting enzyme inhibitor with sacubitril/valsartan once the clinical transition to symptomatic heart failure has occurred.[4,5]

ARTICLE INFORMATION

Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02924727.

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Sources of Funding

PARADISE-MI (Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI) was sponsored by Novartis.

Disclosures

Dr Pfeffer reports research grant support through Brigham and Women's Hospital from Novartis; and consulting fees from AstraZeneca, Boehringer Ingelheim and Eli Lilly Alliance, Corvidia, DalCor, GlaxoSmithKline, National Heart, Lung, and Blood Institute (NHLBI) CONNECTs (Master Protocol Committee), Novartis, Novo Nordisk, Peerbridge, and Sanofi; and has equity in DalCor. Dr Claggett reports consultancy fees from Amgen Inc, Beren Therapeutics, Myokardia, Novartis, and Peerbridge Health. Dr Lewis reports research grant support from Novartis; consulting fees from Amgen, Dal-Cor, and Merck. Dr Granger reports consultancy fees and/or research support from Novartis, AstraZeneca, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Correvio, Daiichi Sankyo Co., Janssen Global Services, and Pfizer Inc. Dr Køber reports consultancy fees from Boehringer Ingelheim. Dr Maggioni reports consultancy fees from Novartis. Dr Mann reports consultancy fees from Bristol-Myers Squibb, Cardurion, LivaNova USA Inc, Novartis, Novo Nordisk, and Renovacor. Dr McMurray reports research grant support through his employer, Glasgow University, from Novartis. Dr Rouleau reports consultancy fees from Novartis Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb and Sanofi-Aventis US, LLC. Dr Solomon reports research grant support through Brigham and Women's Hospital from Actelion Pharmaceuticals, Alnylam Pharmaceuticals, Amgen, AstraZeneca, Bayer, Bellepheron, Bristol-Myers Squibb, Celladon Corporation, Cytokinetics, Eidos, Eli Lilly and Company, GlaxoSmithKline, Ionis, Mesoblast, Myokardia, Neurotronik, Novartis, Novo Nordisk, Respicardia Inc, Sanofi Pasteur Inc, and Theracos; consulting fees from Abbott Vascular, Action Medical Research, Akros, Alnylam Pharmaceuticals, American Regent, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb Eli Lilly and Company, Cardiac Dimensions, Cardior, Cardurion, CellProThera, Cytokinetics, Daiichi Sankyo Company, Genomics, GlaxoSmithKline, Johnson and Johnson, Merck, Moderna, Myokardia, Novartis, Quantum, Roche Diagnostics Corporation, Sanofi Pasteur Inc, Sarepta Therapeutics Inc, Tenaya, Theracos, Tremeau and has equity in Dinaqor; other: Corvia Medical. Dr Steg reports research grant support from Bayer; consulting fees from Amarin Pharma Inc, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen Pharmaceuticals, Novartis, Novo Nordisk, Regeneron Pharmaceuticals, Sanofi US Services Inc, and Servier. Dr Berwanger reports consultancy fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis Pharma, and Pfizer. Dr Cikes reports research support from Abbott and Novartis; and Institutional, Organizational, or Other Financial Benefit from: Abbott, GE Healthcare, Pfizer, and Teva Pharmaceutical Industries. Dr De Pasquale reports consultancy fees from Novartis and Institutional, Organizational, or Other Financial Benefit from Novartis. Dr Landmesser reports research support from Amgen, Bayer, and Novartis; consultancy fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo Company, Novartis, Pfizer, and Sanofi Pasteur Inc. Dr Petrie reports research support from AstraZeneca, Boehringer Ingelheim, Novartis, and SQ Innovation; consulting fees from AstraZeneca, Boehringer Ingelheim, Novartis, Novo Nordisk, SQ Innovation, and Vifor Pharma. Dr Senni reports consulting fees from Abbott Fund, Bayer, Bayer Healthcare, Novartis, Merck, and Vifor Pharma. Dr van d reports research support from AstraZeneca, Pfizer, and Vifor Pharma. Drs Lefkowitz, Zhou, and Wang are full-time employees of Novartis. Dr Braunwald reports research grant support through Brigham and Women's Hospital from AstraZeneca, Daiichi-Sankyo, Merck, and Novartis; consulting for Amgen, Boehringer-Ingelheim/Lilly, Cardurion, MyoKardia, NovoNordisk, and Verve. The other authors report no conflicts.

REFERENCES

1. Jering KS, Claggett B, Pfeffer MA, Granger C, Køber L, Lewis EF, Maggioni AP, Mann D, McMurray JJV, Rouleau JL, et al. Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics. *Eur J Heart Fail.* 2021;23:1040–1048. doi: 10.1002/ejhf.2191
2. Pfeffer MA, Claggett B, Lewis EF, Granger CB, Køber L, Maggioni AP, Mann DL, McMurray JJV, Rouleau J-L, Solomon SD, et al. Angiotensin receptor-neprilysin inhibition in acute myocardial infarction. *N Engl J Med.* In press. doi: 10.1056/NEJMoa2104508
3. Pocock SJ, Stone GW. The primary outcome fails - what next? *N Engl J Med.* 2016;375:861–870. doi: 10.1056/NEJMra1510064
4. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371:993–1004. doi: 10.1056/NEJMoa1409077
5. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 2019;380:539–548. doi: 10.1056/NEJMoa1812851