Author's Reply: Response to_ Defining comparators according to IQWIG's efficiency-frontier method

van der Pol, Simon; Jong, de, Lisa; Vemer, Pepijn; Jansen, Danielle; Postma, Maarten

Published in:
Value in Health

DOI:
10.1016/j.jval.2019.12.013

Publication date:
2020

incremental costs and benefits of current care compared with historical or no treatment carries a non-negligible uncertainty, which would need to be reflected in the willingness to pay for sacubitril/valsartan. Using information both on the adjusted annual treatment cost of 'current' care as well as the incremental costs and benefits compared with a historical treatment group, one could arrive at a corridor for the price of sacubitril/valsartan expressing the uncertainty for decision making (cf.[8]).

In summary, although the article by van der Pol et al[1] raises an important issue, it is potentially solvable based on the existing guidance provided by the IQWiG. For this reason, the conclusion must not be that the EF method is not applicable in this situation. Rather, it is a question of finding another comparator for enalapril and even using data on historical treatment or the natural disease course for this matter. Therefore, although the authors present a thought-provoking conundrum, it does not necessarily present an omission in the EF methodology.

REFERENCES

1. van der Pol S, de Jong LA, Vemer P, Jansen DEMC, Postma MJ. Cost-effectiveness of sacubitril/valsartan in Germany: an application of the efficiency frontier. *Value Health*. 2019;22(10):1119–1127.
2. Gandjour A. A proportional rule for setting reimbursement prices of new drugs and its mathematical consistency. *BMC Health Serv Res*. 2020 (in press).
3. Gandjour A, Chernyak N, Icks A, Gafni A. Public acceptance of different approaches to determine drug reimbursement prices and whether it is influenced by framing: an empirical evaluation in Germany. *Int J Public Sector Manage*. 2014;27(6):501–511.
4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *General methods: version 5.0*. Cologne, Germany; 2017.
5. Krikler DM. The foxglove, "The old woman from Shropshire" and William Withering. *J Am Coll Cardiol*. 1985;5(5 suppl A):3A–9A.
6. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356(23):2388–2398.
7. Gandjour A, Ostwald DA. Sacubitril/valsartan (LCZ696): a novel treatment for heart failure and its estimated cost effectiveness, budget impact, and disease burden reduction in Germany. *Pharmacoeconomics*. 2018;36(10):1285–1296.
8. Stollenwerk B, Lhachimi SK, Briggs A, et al. Communicating the parameter uncertainty in the IQWiG efficiency frontier to decision-makers. *Health Econ*. 2015;24(4):481–490.

Author's Reply

Simon van der Pol, PharmD,[1,*] Lisa A. de Jong, PharmD,[2] Pepijn Vemer, PhD,[2,3] Danielle E.M.C. Jansen, PhD,[1,4] Maarten J. Postma, PhD[1,5]

[1]Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [2]Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands; [3]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [4]Department of Sociology, Interuniversity Center for Social Science Theory and Methodology (ICS), University of Groningen, Groningen, The Netherlands; [5]Institute of Science in Healthy Aging and Healthcare, University Medical Center Groningen, University of Groningen, Groningen Research Institute of Pharmacy, Groningen, The Netherlands[1]

We would like to thank the author for taking the time to formulate a response to our article.[1] It raises an important topic, namely, the choice of comparators when applying the German efficiency frontier (EF) approach. In any economic evaluation, defining the comparators will greatly influence the results and conclusions. Because constructing an EF depends on at least 2 comparators, while also affecting the willingness-to-pay threshold, the influence of these comparators is increased further. The author casts some doubts on whether the comparators we used are sufficient to support our conclusions regarding the applicability of the EF and suggests it may be relevant to include historical treatment in the analysis. The author also mentions the natural disease course but agrees that this "may be difficult to obtain, given that the still-approved drug digitalis has been around for centuries."[1]

We compared 4 different treatment strategies for heart failure patients with a reduced ejection fraction (HF-rEF)—placebo, enalapril (representing angiotensin-converting enzyme inhibitors), candesartan (representing angiotensin receptor blockers), and sacubitril/valsartan (a new class of drugs, angiotensin receptor neprilysin inhibitors)—using 3 randomized clinical trials[2–4] to model the clinical effects. Although this is not stated explicitly in our article, all these trials considered these treatment options against a background of (at that time) current treatment.[2–4] The treatment we refer to as placebo in fact can be referred to as historical treatment because the SOLVD treatment trial compared 2 arms: placebo and standard treatment to enalapril and standard treatment.[4,5] Regarding the costs, we considered that the PARADIGM-HF trial provided the most up-to-date data on background medicine use for HF-rEF patients and included €12.36 per patient per month.[1]

This brings us to the clinical decision problem that underlies our model, which is whether sacubitril/valsartan should be prescribed to HF-rEF patients instead of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker therapy against a background of otherwise optimal heart failure treatment. The included comparators as well as sacubitril/valsartan are highly unlikely to be considered as monotherapy for symptomatic HF-rEF patients[6] and are also mutually exclusive (ie, they should not be combined and are true alternatives to each other, see Caro et al[7]). We believe the comparison of the 4 included strategies not only is best supported by clinical evidence,[8] but also there is also no medical relevance to include different strategies in the EF.[6] This is the reason why we included these 4 treatment options in the EF.

As mentioned by the author, we can conclude that our analysis is an example of one of the 2 special constellations as described by IQWiG,[9] where enalapril is the origin (as it dominates historical treatment) and "a recommendation for a new intervention cannot be directly inferred on the basis of the EF."[9] We believe this is a relevant drawback of this approach because this may occur for other innovative drugs that can only be compared to generic drugs. Nevertheless, as stated in our article, we do believe the EF approach may have benefits when combined with

* Address correspondence to: Simon van der Pol, PharmD, Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. Email: s.van.der.pol@rug.nl

1098-3015/$36.00 - see front matter
https://doi.org/10.1016/j.jval.2019.12.013

regular cost-effectiveness analyses.[1] Therefore, we suggest the EF approach as a complementary approach to cost-effectiveness analysis rather than an alternative.

Acknowledgments

Maarten J. Postma received grants and honoraria from various pharmaceutical companies, including the company marketing the drug of interest in this paper.

This study was however not financially supported and performed at our own initiative.

REFERENCES

1. van der Pol S, de Jong LA, Vemer P, Jansen DEMC, Postma MJ. Cost-effectiveness of sacubitril/valsartan in Germany: an application of the efficiency frontier. *Value Health*. 2019;22(10):1119–1127.
2. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004.
3. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362(9386):772–776.
4. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293–302.
5. The SOLVD Investigators. Studies of Left Ventricular Dysfunction (SOLVD)—rationale, design and methods: two trials that evaluate the effect of enalapril in patients with reduced ejection fraction. *Am J Cardiol*. 1990;66(3):315–322.
6. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). *Nationale VersorgungsLeitlinie Chronische Herzinsuffizienz – Langfassung (3rd edition)*. www.herzinsuffizienz.versorgungsleitlinien.de. Accessed November 20, 2019.
7. Caro JJ, Nord E, Siebert U, et al. The efficiency frontier approach to economic evaluation of health-care interventions. *Health Econ*. 2010;19(10):1117–1127.
8. McMurray J, Packer M, Desai A, et al. A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure. *Eur Heart J*. 2015;36(7):434–439.
9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. General methods: version 5.0. https://www.iqwig.de/en/methods/methods-paper.3020.html. Accessed July 17, 2018.