PIPC Partnership to Improve Patient Care

August 20, 2019

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

On behalf of the Partnership to Improve Patient Care (PIPC), we are writing to provide comments on the Institute for Clinical and Economic Review's (ICER) draft evidence report on treatments for Cardiovascular Disease (CVD). CVD kills more Americans each year than any other disease.[1] With this in mind, it is particularly important that effective treatments are available to patients. The methodological flaws in ICER's report are concerning, especially the suggestion that only 2% of eligible patients should have access to highly effective treatments, which is both unethical and illogical.

We would like to highlight the following concerns with ICER's report:

ICER's Budget Impact Threshold is Unethical and Illogical

The budget impact model explicitly states the percentage of eligible patients that could be treated in a given year, noting that only 2% of eligible patients could be treated with rivaroxaban without crossing the budget threshold and only 2% of eligible patients could be treated with icosapent ethyl without crossing the budget threshold. While ICER claims that its budget impact model is not a budget cap, its sole purpose appears to be to recommend to payers that they impede patient access as a way to limit spending on treatments. In that sense, ICER's budget threshold is indistinguishable from a budget cap on new drug spending. If ICER's true goal was to simply provide payers with information on the impact treatments will have on their budgets, no threshold is necessary.

Not only does rationing present an ethical problem by suggesting that only 2% of eligible patient should receive treatment for a disease, it is also illogical. Use of effective interventions (which even by ICER's admission, these are) leads to fewer costly adverse events and avoidable health spending, improving quality of life, and increasing productivity, both for patients and for the health system. While reductions in health care spending are certainly necessary, our goal should be to eliminate care that is less effective, and less valuable to patients, rather than applying a blunt threshold to innovative treatments.

[1] American Heart Association. Cardiovascular Disease. Accessed July 30, 2019.

It is also problematic that ICER's budget impact model assumes a take-up rate of 100% over five years for these new drugs, which assumes that every single person that could theoretically benefit from these interventions will ultimately receive it. This flawed logic has been proven incorrect time and time again, yet ICER persists in making this assumption. A prime example of this was ICER's budget impact model for PCSK9 inhibitor drugs in 2015.[2] This report also relied on the unrealistic assumption of full take-up over five years. Four years later the take-up rate of PCSK9 inhibitors is estimated to be less than 1%.[3]

ICER Incorrectly Assumes There is No Quality of Life Impact from Interventions

ICER assumes there is zero "quality of life" impact from these interventions despite a growing body of evidence that successful treatment of CVD risk factors has had strong effects on psychological well-being and quality of life beyond gains associated purely with their event risk effects, or movements across health states. The ICER model disregards these effects.

For example, a recent study in long term statin users showed lower depression, anxiety, and hostility after adjustment for the propensity for statin use and potential confounders. The beneficial psychological effects of the statins appeared to be independent of the drugs' cholesterol-lowering effects.[4] Patients with high blood pressure have seen similar results.[5]

ICER even acknowledges that there is ongoing research into quality of life through COMPASS and notes that at the time of this report the data is not yet available. It is frustrating that ICER continues to translate "yet to report findings" into "no effect," which is frequently not accurate.

ICER Uses an Artificially Narrow Definition of Major Adverse Cardiovascular Event

ICER chooses to use an incredibly narrow definition of Major Adverse Cardiovascular Event (MACE) in its base case, despite it being well known how MACE is defined and what events are included that have a significant impact on outcomes.[6] The definition of MACE in the base case is a shorthand version including only myocardial infarction (MI), stroke and CVD death. A wider and more appropriate definition of MACE that includes revascularization and unstable angina is used in the sensitivity analysis. It is unsurprising that the analysis using a full and appropriate definition of MACE shows much more beneficial effectiveness results. What is surprising is that

[2] See https://icer-review.org/wp-content/uploads/2016/01/Final-Report-for-Posting-11-24-15-1.pdf
[3] Chamberlain AM, Gong Y, Shaw KM, Bian J, Song WL, Linton MF, Fonseca V, Price-Haywood E, Guhl E, King JB, Shah RU. PCSK9 Inhibitor Use in the Real World: Data From the National Patient-Centered Research Network. Journal of the American Heart Association. 2019 May 7;8(9):e011246.
[4] Young-Xu Y, Chan KA, Liao JK, Ravid S, Blatt CM. Long-term statin use and psychological well-being. Journal of the American College of Cardiology. 2003 Aug 20;42(4):690-7.
[5] Croog SH, Levine S, Testa MA, Brown B, Bulpitt CJ, Jenkins CD, Klerman GL, Williams GH. The effects of antihypertensive therapy on the quality of life. New England Journal of Medicine. 1986 Jun 26;314(26):1657-64.
[6] Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. Journal of the American College of Cardiology. 2008 Feb 19;51(7):701-7.

despite these results, ICER actively chose to use the less comprehensive measure of MACE in the base case.

ICER's Model Uses Inappropriate Data for the Population Being Treated with These Drugs

The source of ICER's data comes from a CVD risk calculator constructed from the Framingham Heart Study (D'Agostino et al 2008),[7] which uses data from a less diverse population to estimate the relative risk of a series of CVD events, such as stroke, MI and CVD death than in the general population. There is detailed literature as to why this risk calculator tends to significantly underestimate risk for a more generalized population.[8] There are two key reasons this particular risk calculator is a bad fit for this research question:

1. Using this risk framework, ICER's model assesses the probability of a CVD event in a primary prevention population, whereas the drugs being evaluated are likely to be used more commonly on a secondary prevention population - those who have been diagnosed with coronary artery disease (CAD) or peripheral artery disease (PAD) or have experienced a previous cardiovascular event. The populations who are likely to benefit from these drugs are therefore likely to have much higher relative risk of future CVD events than the population used to construct the risk calculator. As a result, any absolute estimate of effect using this risk calculator will be an underestimate the absolute risk reduction for the population that is likely to benefit.
2. The risk calculator from which the ICER model is derived uses data from ages 30 to74 only, but the proportion of people being treated for CVD in the general population who are over 74 years of age is almost 50% and rising. Thus, information derived from the risk calculator does not paint an accurate picture of the patient population for which ICER is assessing treatments. In fact, the American Heart Association has endorsed aggressive secondary prevention of CVD events in adults older than 75 years of age, recognizing that the risk of several forms of atherosclerotic CVD, including stroke and MI, rise significantly with age.[9] In addition to inappropriate age representation, the study was not representative of CVD patients in terms of race or gender. The REDUCE-IT population was less than 30% female, and less than 10% people of color, thus, important populations are underrepresented. Research has demonstrated a significant racial health disparity in CVD. By failing to include data that properly reflects these subpopulations risk and likely outcomes, ICER is contributing to furthering these health disparities.

[7] D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care. Circulation. 2008 Feb 12;117(6):743-53.
[8] Jørstad HT, Colkesen EB, Boekholdt SM, Tijssen JG, Wareham NJ, Khaw KT, Peters RJ. Estimated 10-year cardiovascular mortality seriously underestimates overall cardiovascular risk. Heart. 2016 Jan 1;102(1):63-8.
[9] Kozak LJ, DeFrances CJ, Hall MJ. National hospital discharge survey: 2004 annual summary with detailed diagnosis and procedure data. Vital and health statistics Series 13, Data from the National Health Survey. Atlanta, GA: National Center for Health Statistics; 2006:1-209

The use of the Framingham Heart Study, instead of real-world data, in constructing the risk calculator had led to serious shortcomings in ICER's model. The cost-effectiveness methodology literature has been consistent over recent years in emphasizing the need to use real word data sources where possible for baseline risk data[10, 11] and for cost-effectiveness modeling,[12] not risk calculators constructed from non-representative populations such as the Framingham Heart Study,[13,14] which is far from reflective of the true risk of a generalized population. We would strongly advise ICER to change its sources for baseline risk and re-run its estimates of effectiveness and ultimately cost-effectiveness using a real world data source that encompasses the entire population of need who could benefit from such drugs, such as the one derived from the REACH registry.[15]

Conclusion

ICER continues to use a flawed methodology, ignoring real-world data and quality of life outcomes that matter to patients in favor of data that easily crosswalks into the discriminatory QALY metric. We urge ICER to reconsider both its data sources and its concerning theory that health care must be rationed to achieve savings and efficiency in our health care system.

Sincerely,

Tony Coelho
Chairman, Partnership to Improve Patient Care

[10] Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103.
[11] Makady A, ten Ham R, de Boer A, Hillege H, Klungel O, Goettsch W. Policies for use of real-world data in health technology assessment (HTA): a comparative study of six HTA agencies. Value in Health. 2017 Apr 1;20(4):520-32.
[12] Cohen AT, Goto S, Schreiber K, Torp-Pedersen C. Why do we need observational studies of everyday patients in the real-life setting?. European Heart Journal Supplements. 2015 Jul 1;17(suppl_D):D2-8.
[13] Lee GK, Lee LC, Liu CW, Lim SL, Shi LM, Ong HY, Lim YT, Yeo TC. Framingham risk score inadequately predicts cardiac risk in young patients presenting with a first myocardial infarction. Ann Acad Med Singapore. 2010 Mar 1;39(3):163-7.
[14] Michos ED, Nasir K, Braunstein JB, Rumberger JA, Budoff MJ, Post WS, Blumenthal RS. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. Atherosclerosis. 2006 Jan 1;184(1):201-6.
[15] Wilson PW, D'Agostino Sr R, Bhatt DL, Eagle K, Pencina MJ, Smith SC, Alberts MJ, Dallongeville J, Goto S, Hirsch AT, Liau CS. An international model to predict recurrent cardiovascular disease. The American journal of medicine. 2012 Jul 1;125(7):695-703