Editorial Comment

"Drugs Do Not Work on Patients Who Do Not Take Them" Can We Do Better in Patient Adherence?

KEMAR J. BROWN, MD,[1,2] AND HANNA K. GAGGIN, MD, MPH[1,2]

Boston, Massachusetts

Beta blockers are one of the cornerstones drugs in the pharmacopeia of Guideline-Directed Medical Therapy (GDMT) currently used to improve outcomes in patients with heart failure (HF) with reduced ejection fraction (HFrEF).[1] However, real life use and dose up-titration of GDMT beta blockers remain quite dismal.[2] In the current issue of the Journal, Loop et al[2] report that only 38% of hospitalizations for acute decompensated HF were followed by a prescription refill of a GDMT beta blocker within 30 days of discharge, only 12% of patients were at ≥50% of recommended dose within 1 year, and only 9% of patients had their beta blockers up-titrated within that same year. Although there are numerous studies that evaluate HFrEF medication adherence from the perspective of physicians and hospitals (ie, prescriptions written or patient-reported medication lists, which are expected to show higher adherence), the data generated by Loop and colleagues[2] may more accurately reflect the use of refilled medications taken by our patients in the real world. The numbers are sobering, particularly because beta blockers have been shown to improve symptoms, hemodynamics, exercise capacity, left ventricular remodeling indices, and ejection fraction, and are associated with a dramatic 35% relative risk reduction for mortality with concurrent reduction in HF hospitalizations.[3–5]

Based on results from registries that evaluated written prescriptions or patient reports and were aimed at improving adherence to GDMT in HF (eg, IMPROVE-HF or CHAMP-HF), adherence to beta blockers did not improve much over time. In addition, only 67% of patients without contraindications were prescribed a GDMT beta blocker, and 28% of these were dosed to clinical trial targets in the CHAMP-HF Registry.[6] Although one could argue that heart rate should be the true determinant of target dose, benefits of beta blockers were dose-dependent in clinical trials. Even in highly-selected patients in contemporary, randomized control trials with rigorous follow-up and highly-motivated and compliant patients such as the GUIDE-IT study, only 60% of patients achieved at least 50% of GDMT beta blocker dose with 15% achieving 100% of clinical trial target dose at 1 year.[7]

In the past few years, novel medications such as sacubitril/valsartan and ivabradine with proven mortality and/or hospitalization benefits have also been approved but uptake into clinical practice has been slow.[8] As Greene et al point out, the main reason for failure to use these drugs is not because of lack of treatment options, rigorous follow-up or motivation to up-titrate[6]; non-adherence may play a vital role. A systematic focus on therapy adherence must be prioritized in order to effect innovative and intentionally disruptive change at the level of the patient and family, amongst health-care providers, within the health system, the local community, and regionally/nationally at the level of our policy makers (Fig. 1).

Several targeted interventions have been shown to improve adherence including repetitive and individualized patient education, simplified medication regimens such as using combination pills and reminders about medications or health behaviors. They are designed to use incentives to reinforce positive behavior and may help to remove social and financial barriers and foster accountability.[9,10] Social and cultural influences in medical management cannot be ignored; for example, having a pharmacist involved in blood pressure monitoring and medication titration in collaboration with physicians at black-owned barbershops resulted in a dramatic reduction in systolic blood pressure.[11] This favorable outcome may be the result of delivering care in a nontraditional health-care setting where nonjudgmental and open conversations are encouraged and a lot of community socialization happens.

Use of mobile applications and telehealth platforms to improve adherence also holds promise because the majority of Americans now own smart phones and there has been a dramatic increase in the availability of patient-centered mobile health applications. These approaches may allow

From the [1]Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts and [2]Harvard Medical School, Boston, Massachusetts.

Reprint requests: Hanna K. Gaggin, MD, MPH, Cardiology Division, Massachusetts General Hospital, 55 Fruit Street, Yawkey 5B, Boston, MA 02114. E-mail: hgaggin@mgh.harvard.edu

Funding: Dr. Gaggin is supported in part by the Clark Fund for Cardiac Research Innovation.

See page 354 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.04.003

Fig. 1. Established, innovative and disruptive concepts that may improve patient medication adherence at the level of the patient and family, amongst health-care providers, within the health system and the local/regional/national government level.

for rapid communication with physicians, facilitate remote monitoring of vital signs and adverse drugs effects, and facilitate virtual visits.[12,13] However, clinicians have been slow to get involved in developing and testing mobile applications and many of these platforms are not well-validated. It is also important to highlight that elderly patients or patients with limited socioeconomic resources may not have facile access to such technology. Several mobile applications are targeted for physicians including the *TreatHF and ICD-CRT Appropriate Use Criteria* and *Guideline Clinical* from the American College of Cardiology, which may add more value than electronic health record-linked reminders. With the creation and utilization of machine learning and artificial intelligence technology, we may be able to use these models to develop best practices for patient management.[14]

A 15−30 minute follow-up visit with a physician is not long enough to adequately address medication adherence as well as clinical needs in complex medical patients. However, the use of multidisciplinary teams designed to manage complex chronic disorders may help to address the problem. For example, pharmacists and nurses can assist in patient education and co-management, and counselors and psychiatrists can work with patients to address cognitive and psychiatric barriers to adherence. In this context, novel approaches to coronary heart disease management are being tested by One Brave Idea, a unique joint venture of an academic team at Brigham and Women's Hospital, the American Heart Association, Verily (formerly Google Life Sciences), and a pharmaceutical company, AstraZeneca, that may be applicable in HF management.[15] The approach being tested includes deep phenotyping using genomic, biomarker and big data, assay development for early detection, engagement of a broad patient population in research through digital technology and promotion of nontraditional partnerships.

Additionally, family- and community-based multidisciplinary intervention initiatives, such as the FAMILIA project, can target high-risk populations to address behavioral and cultural attitudes toward cardiovascular health.[16]

Lastly, government stewardship of adherence will be paramount in order to facilitate paradigm shifts in accountable delivery of GDMT in HFrEF. As Loop et al[2] point out, inventive reimbursement policies by the Centers for Medicare and Medicaid Services (CMS) that target and incentivize prescription fills in HFrEF population may improve clinical outcomes. For now, although there are national initiatives that include tools to improve adherence designed to prevent and treat myocardial infarction and strokes, such as the Million Hearts led by the Centers for Disease Control and Prevention and CMS there are no correlates for patients with HF.[17]

Despite some limitations to the methodology of the current study, mainly inherent in all CMS data studies (eg, unknown written prescription rate, exclusion of beneficiaries with Medicare Advantage [Part C], absence of direct documentation of contraindications and inclusion of a relatively small portion of CMS beneficiaries), Loop et al clearly demonstrate persistent under-utilization of GDMT beta blockers in a large cohort. Their study should serve as a reminder that although we have made tremendous strides in discovering therapy to halt and even reverse cardiac remodeling in HF, we have yet to fully tackle the obstacles that prevent appropriate delivery of lifesaving treatment.

Disclosures

Dr. Brown has no disclosures. Dr. Gaggin has received a research grant support from Roche Diagnostics, Jana Care, Ortho Clinical, Novartis; consulting income from Merck, Roche Diagnostics; research payments for clinical endpoint committees from Radiometer.

References

1. Yancy Clyde W, Jessup M, Bozkurt B, Butler J, Casey Donald E, Colvin Monica M, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137–e61.
2. Loop MS, van Dyke MK, Chen L, Safford MM, Kilgore ML, Brown TM, et al. Low utilization of beta-blockers among medicare beneficiaries hospitalized for heart failure with reduced ejection fraction. J Card Fail 2019;25:343–51.
3. Metra M, Nardi M, Giubbini R, Dei Cas L. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1994;24:1678–87.
4. Fonarow GC, Hernandez AF, Solomon SD, Yancy CW. Potential mortality reduction with optimal implementation of angiotensin receptor neprilysin inhibitor therapy in heart failure. JAMA Cardiol 2016;1:714–7.
5. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure: a Bayesian meta-analysis. Ann Intern Med 2001;134:550–60.
6. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. J Am Coll Cardiol 2018;72:351–66.
7. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2017;318:713–20.
8. Dierckx R, Cleland JGF, Parsons S, Putzu P, Pellicori P, Dicken B, et al. Prescribing patterns to optimize heart rate: analysis of 1,000 consecutive outpatient appointments to a single heart failure clinic over a 6-month period. JACC Heart Fail 2015;3:224–30.
9. Chang Leslie L, DeVore Adam D, Granger Bradi B, Eapen Zubin J, Ariely D, Hernandez Adrian F. Leveraging behavioral economics to improve heart failure care and outcomes. Circulation 2017;136:765–72.
10. Kini V, Ho PM. Interventions to improve medication adherence: a review. JAMA 2018;320:2461–73.
11. Victor RG, Lynch K, Li N, Blyler C, Muhammad E, Handler J, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. N Engl J Med 2018;378:1291–301.
12. Sharma A, Harrington RA, McClellan MB, Turakhia MP, Eapen ZJ, Steinhubl S, et al. Using digital health technology to better generate evidence and deliver evidence-based care. J Am Coll Cardiol 2018;71:2680–90.
13. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658–66.
14. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med 2019;25:44–56.
15. Cranley J, MacRae CA. A new approach to an old problem: one brave idea. Circ Res 2018;122:1172–5.
16. Bansilal S, Vedanthan R, Kovacic JC, Soto AV, Latina J, Björkegren JLM, et al. Rationale and design of Family-Based Approach in a Minority Community Integrating Systems-Biology for Promotion of Health (FAMILIA). Am Heart J 2017;187:170–81.
17. Frieden TR, Berwick DM. The "Million Hearts" Initiative: preventing heart attacks and strokes. N Engl J Med 2011;365:e27.