Lessons from the trials

STOP-HF: Expanding the role of HF programs into the community

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ABSTRACT
The St Vincent’s Screening TO Prevent Heart Failure (STOP-HF) study is a recently published trial that assessed the use of brain natriuretic peptide (BNP) as a screening tool for HF in an at-risk population in reducing newly-diagnosed heart failure and prevalence of significant left ventricular (LV) systolic and/or diastolic dysfunction. The study provides an excellent model to the global community on how to integrate primary care simple screening with secondary and tertiary level targeted diagnostic and therapeutic system. This integration includes screening of high-risk groups, use of a sensitive screening tool, early diagnostic modalities, early therapeutic interventions, and proper assessment of the hard clinical outcomes. However, more studies are needed across multiple sites around the world with different levels of health care services and variable biomarkers to identify higher-risk groups.
PROLOGUE
The last fifty years have witnessed remarkable improvement in the morbidity and mortality trends of most cardiovascular diseases. However, heart failure (HF) remains a notable exception. HF is a growing global health problem in both industrialized and developing nations. In fact, HF is the second most common cause for hospital admissions; the first cause is normal delivery. In the United States, the number of people with HF is expected to rise 46 percent from 5 million in 2012 to 8 million in 2030. The rise in patient numbers will double the costs of HF treatment, from $31 billion in 2012, to a staggering $70 billion in 2030. These facts have stimulated the search for new effective methods to combat HF. An attractive strategy is to integrate the early detection of high-risk patients at the primary care level with advanced diagnostic and therapeutic strategies at the tertiary care level.

The St Vincent’s Screening TO Prevent Heart Failure (STOP-HF) study is a recently published trial in the Journal of American Medical Association (JAMA) assessing the use of brain natriuretic peptide (BNP) as a screening tool for HF in an at-risk population in reducing newly-diagnosed heart failure and prevalence of significant left ventricular (LV) systolic and/or diastolic dysfunction.

STOP-HF TRIAL DESIGN AND RESULTS
In this “first-of-its-type” study, the investigators recruited 1374 participants with various cardiovascular risk factors from a nurse-provided primary care cardiovascular screening program in the catchment area of St Vincent’s University Hospital, Dublin, Ireland, between January 2005 and December 2009. Eligibility criteria were age older than 40 years (mean age, 64.8 [SD, 10.2] years) and a history of one or more of the following; hypertension, hypercholesterolemia, obesity, vascular disease, diabetes mellitus, arrhythmias, moderate to severe valvular heart disease. Exclusion criteria included refusal to consent, established evidence of LV systolic dysfunction, history of symptomatic HF, or a diagnosis compromising survival over the study period.

The participants were randomly assigned to receive the usual primary care (control condition; \( n = 677 \)) or screening with BNP testing (\( n = 697 \)) and followed up until December 2011 (mean follow-up, 4.2 [SD, 1.2] years). Intervention-group participants, with BNP levels of 50 pg/mL or higher, underwent echocardiography and collaborative care between their primary care physician and specialist cardiovascular service.

The primary end point was prevalence of asymptomatic systolic LV dysfunction, with or without newly diagnosed heart failure. Due to the slower than expected recruitment rates, the investigators extended the study period and redefined the primary endpoint to include significant LV diastolic dysfunction as determined by a ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E’) greater than 15. It is important to note that this change did not alter the validity of the study design. Secondary end points included emergency hospitalization for arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or heart failure. The inclusion of asymptomatic LV systolic dysfunction or significant diastolic dysfunction as a component of the primary endpoint reflect the heightened risk status of these abnormalities, specifically to the later development of HF.

A total of 263 patients (41.6%) in the intervention group had at least 1 BNP reading of 50 pg/mL or higher. Of the risk factors included in the study, this finding was consistent with the increasing age of the population. As expected, the intervention group underwent more cardiovascular investigations and received more renin-angiotensin-aldosterone system-based therapy at follow-up. The primary end point of left ventricular dysfunction with or without HF was met in 59 patients (8.7%) in the control group and 37 patients (5.3%) in the intervention group (odds ratio [OR], 0.55; 95% CI, 0.37–0.82; \( P = 0.003 \)). Asymptomatic LV dysfunction was found in 45 (6.6%) of 677 control-group patients and 30 (4.3%) of 697 intervention-group patients (OR, 0.57; 95% CI, 0.37–0.88; \( P = 0.01 \)). HF occurred in 14 (2.1%) of 677 control-group patients and 7 (1.0%) of 697 intervention-group patients (OR, 0.48; 95% CI, 0.20–1.20; \( P = 0.12 \)). The incidence rates of emergency hospitalization for major cardiovascular events were 40.4 per 1000 patient-years in the control group versus 22.3 per 1000 patient-years in the intervention group (incidence rate ratio, 0.60; 95% CI, 0.45–0.81; \( P = 0.002 \)).

CRITIQUE
STOP-HF is the first prospective, randomized trial to demonstrate reduction in adverse cardiovascular clinical outcomes using BNP guided collaborative care in a broad community cohort. BNP blood level has
long been established as an important diagnostic and prognostic tool in the management of HF. BNP is stored in the ventricles, and to a lesser extent in the atria. High ventricular filling pressures stimulate the release of BNP which has a diuretic, natriuretic, and antihypertensive effect by inhibiting the renin-angiotensin-aldosterone system. The recent HF guidelines recommend that BNP screening may have some value in populations with certain risk factors such as previous ischemic heart disease, diabetes, and/or hypertension. What was unique about STOP-HF is that it reached beyond the simple confirmation of BNP as a risk predictor of HF. The investigators’ aim was to prevent HF through risk factor modifications using medical, dietary and lifestyle interventions in a high-risk group defined by BNP.

The STOP-HF study raises some interesting points. First, the study highlights the importance of dedicated HF programs to adequately address the global burden of HF. The reduction in LV dysfunction, HF, and HF hospitalization rates observed in the intervention group must be interpreted in the light of the integrated approach utilized in STOP-HF. This multifaceted approach included many risk factors modifiers such as repeated echocardiography and early use of angiotensin receptor blockers. The HF program implemented in St Vincent’s hospital includes specialized clinics with a team of specially trained registered nurses, nurse practitioner, pharmacists, dietician, palliative care specialists and cardiologists. The study results would not be reproducible in other less-than-ideal health care settings.

Second, STOP-HF draws the attention to the importance of including patients with asymptomatic LV systolic dysfunction and significant LV diastolic dysfunction when assessing the overall burden of HF in a population. These two entities may be overlooked in a non-dedicated primary health care set up.

Third, more population-based studies are needed to identify the optimum mean to screen for HF. Other than BNP, many novel markers have proven their efficacy in detecting pathological process associated with early HF such as myocardial stretch (ST2 protein), myocyte injury (high sensitivity troponin assay), and profibrotic process (procollagen type I amino terminal propetide (PINP). Future trials should also target approaches such as genomics, epigenomics, metabolomics and transcriptomics for the discovery of novel biomarkers and disease pathway underlying HF in high-risk populations. For example, high mortality rates have been reported in Indian Asians due to coronary artery disease. In the UK, Indian Asians have two-fold higher coronary heart disease mortality compared to Europeans. The prospective Indian Asian cohorts such as the London Life Sciences Population Study (LOLIPOP) incorporate the “omics” approach to provide an excellent opportunity for the identification of new factors underlying coronary artery disease in this high risk population.

Fourth, a limitation to STOP-HF is that it was underpowered for determination of mortality and all-cause hospitalization outcomes. However, longer follow up analysis (10–15 years) could possibly demonstrate a significant decrease in the death rates in the intervention group. In addition, there were too few events for further sub-group analysis according to age or risk factors. Future larger studies should focus on recognising those who would benefit the most from this proactive screening strategy.

Finally, the cost-effectiveness analysis of this strategy has not yet been reported. A critical question that needs to be answered before adopting a similar screening program on a wider scale is how much this strategy cost? Hopefully, with even more specific target population and widely available screening tools, this strategy may further reduce its cost and optimize its efficacy.

WHAT HAVE WE LEARNT?
STOP-HF provides an excellent model to the global community on how to integrate primary care simple screening with secondary and tertiary level targeted diagnostic and therapeutic system. This integration includes screening of high-risk groups, use of a sensitive screening tool, early diagnostic modalities, early therapeutic interventions, and proper assessment of the hard clinical outcomes. However, to reach for the Holy Grail of reducing the global HF burden, more studies are needed across multiple sites around the world with different levels of health care services. More specific, higher-risk groups may show more benefit from this approach with a lesser cost to the public health systems.

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