The Potential Role of Community-based Registries to Complement the Limited Applicability of Clinical Trial Results to the Community Setting: Heart Failure as an Example

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Background: Clinical trials do not represent community settings, making widespread implementation of evidence-based medicine problematic. New heart failure treatments are an example, as results comparable to those of clinical trials have not been observed in the community. Alternatives to clinical trials could provide useful complementary information.

Objectives and Methods: To review the clinical trials and community experiences in heart failure management by searching Pubmed with key words "observational studies," "clinical trials," and "heart failure," to present the preliminary results of a community-based heart failure registry as a complementary database, and to assess the potential value and limitations of the registry approach.

Results: Recent advances in the treatment of heart failure led to guidelines using clinical trial evidence as the rationale for transferring newer therapeutic technologies to the community practice setting. Implementation of such guidelines is slow, reflecting concerns over applicability of clinical trial results to the community setting. A community-based registry of β-blocker treatment for heart failure showed outcomes comparable to those of clinical trials, despite significant differences between physicians and their patients in these settings.

Conclusion: Registries can complement clinical trials to expedite technology transfer to the community setting.

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Evidence-based medicine relies on results of clinical trials, which may be problematic as clinical trials often do not represent patients or care providers from the broad community practice setting. Clinical trials are carried out by investigators who are usually based in academic centers and have a high degree of experience, specialized training, or interest in the particular clinical problem being investigated. Patients enrolled into these trials are selected by criteria that tend to optimize their responsiveness to the question being investigated. Therefore, the results of clinical trials may not be applicable to the community setting.

The transfer of technology from clinical trials to the community setting occurs slowly, as the "evidence" for evidence-based medicine derives from sources not readily applicable to the community setting. The usual approach for expediting the transfer of new technology to the community setting is to expand efforts aimed at educating about the results of clinical trials and urging their rapid and broad adoption. Inherent in this approach is the assumption that clinical trials alone offer sufficient supportive evidence and rationale. The calls for increased educational efforts often emanate from the clinical trialists, who may have biased confidence in their findings. Therefore, this approach may not consider the shortcomings of clinical trials. Another interpretation of the slow transfer of technology is that the community practitioner has been educated but is skeptical about the applicability of clinical trials results to his or her practice setting. In that case, further education about clinical trial results would likely have little effect.

The objective of this article is to examine the potential role of alternative means, especially registries, as investigative tools for collecting valid and useful information to complement clinical trial data and to expedite the transfer of technology from the clinical trial to the community setting. There exists a so-called efficacy-effectiveness gap in the applicability of clinical trial results, especially in the contexts of managed care, disease management programs, and pharmacoeconomics.[1-3] The limited amount of reliable effectiveness data affects healthcare providers and health policy makers in their ability to make well-informed decisions and formulate recommendations.[1] Heart failure represents an area in which an efficacy-effectiveness gap has been recognized. Therefore, we used heart failure as a model for reviewing the roles of clinical trials and registries. The preliminary results of a registry of patients beginning treatment with

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β-blockers for heart failure are reviewed as an example of these methods.

CLINICAL TRIALS AND COMMUNITY EXPERIENCES IN HEART FAILURE

There have been great advances in our understanding of the pathophysiology of heart failure and its management. The favorable results of new treatments, such as vasodilators, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers, on clinical outcomes have led to the development of heart failure management and treatment guidelines that are being updated at shorter intervals.[4-6] The latest guidelines rely on evidence-based medicine as the rationale for transferring these newer diagnostic and therapeutic technologies from the realm of clinical research to the community setting of practicing cardiologists and primary care providers, neither of whom necessarily has specialized interest or expertise in heart failure. Therefore, the rate and extent of implementation of the latest technologies in the community setting appear limited. The scientific basis for and clinical application of β-blockers in heart failure were the subjects of recent reviews that concluded that "[t]he science supporting β-blockers must be translated into practice safely and rationally if the agents are to achieve their full potential."[7(p883),8]

The concerns in heart failure are that clinical trials are usually carried out by experts in the field and include patients who are predominantly younger white men, selected to have stable symptoms, little comorbidity, and rigidly defined criteria for heart failure (eg, reduced left ventricular ejection fraction). Large-scale community observations indicate that the general population with heart failure contains significantly more women, African Americans, and older patients than those included in clinical trials.[9-11] In addition, almost half of the patients in the community setting have normal systolic function, with possible diastolic dysfunction.[12-14] Furthermore, most of these patients are managed by primary care providers who are not cardiologists or do not have specialized expertise or interest in heart failure. In fact, the ability to replicate the apparent improvements in the management and outcomes of heart failure outside the clinical trial setting has been questioned, as results comparable to those reported from clinical trials have not been observed in the broad community, especially among groups inadequately represented in the clinical trials.[15-19] The most recent heart failure management guidelines recognize this problem and call for further investigation in subpopulations with heart failure.[6]

A β-BLOCKER HEART FAILURE REGISTRY

When carvedilol became the first β-blocker approved for use in heart failure in the United States, there was a reluctance among practitioners to use it in the community setting, because β-blockers were previously thought to be contraindicated in heart failure and it was perceived as difficult to apply this new therapeutic technology safely and effectively. Therefore, a β-blocker heart failure registry was designed and implemented to enroll patients starting a regimen of carvedilol for heart failure in the usual care setting and to follow them with prospective longitudinal observations.

Complete details of the registry design have been published elsewhere.[20] Specific objectives were to collect outcomes data and to observe the experience using a β-blocker, carvedilol, in unselected patients with heart failure managed by community physicians in their usual practice without a structured protocol. There were no patient selection criteria other than that patients must be adults starting a regimen of carvedilol for heart failure. The decision to prescribe carvedilol was at the discretion of the participant physician, without applying any prespecified eligibility criteria. The physicians participating in the registry were selected to be representative of community practitioners in the United States and Canada. They included cardiologists and primary care physicians, and special care was taken to minimize the inclusion of physicians from academic settings or with a special interest in heart failure. There was no prespecified schedule of visits or procedures to be followed, as patients were seen according to the usual practice of the participant physician, who performed only those procedures or assessments (eg, echocardiograms and laboratory tests) per his or her usual practice. Information about patient status was recorded at baseline, at the end of carvedilol titration, and as close as possible to 6 and 12 months after completing titration. It is assumed, although not specified, that patients with heart failure would be seen at least at these intervals per standards of good clinical practice. The information recorded included survival status, New York Heart Association (NYHA) class, current medications, clinical or adverse events, and other relevant assessments the physician may have made. Detailed information on the carvedilol dose titration experience was collected.

The registry was completed and analyzed. Characteristics of patients and physicians in the registry and the primary results have been preliminarily reported, comparing groups within the registry and examining registry results relative to those of the carvedilol clinical trials experience in the United States.[21-24] There were 4280

patients enrolled, with 259 cardiologists enrolling 3121 patients and 129 primary care physicians enrolling 1159 patients. Both physician groups had prior experience with use of β-blockers in the treatment of heart failure, but that experience was considered extensive by more cardiologists than primary care physicians. The primary care physicians enrolled more women, African Americans, patients with diabetes mellitus or hypertension, and patients who were older. Their patients also had higher left ventricular ejection fractions. The patients of cardiologists were more likely to be receiving background therapy with a combination of ACE inhibitors, diuretics, and digitalis. The duration of carvedilol titration and the reported degree of difficulty with titration were similar in both groups. Fewer patients managed by primary care physicians achieved recommended maximal target maintenance doses of carvedilol (25 or 50 mg twice daily), but they were less likely to discontinue carvedilol. Therefore, there were significant differences between physician profiles, the baseline characteristics of their patients, and their titration experience with carvedilol in the setting of this β-blocker registry. These differences may reflect heart failure management in general in the community and might be expected to affect the overall results of the registry.

Important differences were also observed when these same types of characteristics were compared between the registry and the carvedilol clinical trials experience. Physicians in the registry were less likely to have an academic affiliation, be hospital-based, or be cardiologists. Patients in the registry were significantly older, included more women, had higher left ventricular ejection fractions, and were less likely to have NYHA class III or IV symptoms. Fewer registry patients were receiving ACE inhibitors, digoxin, or diuretics at baseline compared with those in clinical trials in which background therapy was prespecified per protocol. Although no or little difficulty with carvedilol titration was reported in 83% of patients in the registry, registry patients took longer to complete titration than those in clinical trials. In addition, fewer registry patients achieved the maximal target maintenance doses of carvedilol compared with patients in clinical trials, and more patients in the registry discontinued carvedilol.

Despite the observed differences within the registry between physician profiles, the characteristics of their patients, and the dosing of carvedilol, there was no significant difference in 1-year all-cause mortality between patients treated by cardiologists vs primary care physicians (6.5% vs 7.5%, $P = .33$). In addition, in both groups of patients, hospitalizations for heart failure were reduced by 42% from the year before entering the registry.

In summary, these preliminary results suggest that this β-blocker registry recruited physicians and patient groups who differ significantly from each other and from clinical investigators and patients in heart failure clinical trials. Despite such differences, the all-cause mortality and heart failure hospitalization rates were comparable between patient groups within the registry and were in the same range as those observed in carvedilol clinical trials.[24] Therefore, the differences in patient populations and their risk factors were unimportant prognosticators, or they tended to cancel each other out. This registry provides a large prospective database evaluating a recently approved heart failure treatment (at the time of registry development) in the community setting and demonstrates the key role that community-based healthcare providers can fulfill as clinical investigators outside the traditional clinical trials setting.

ALTERNATIVES TO CLINICAL TRIALS

Whereas the preliminary results of the registry described in the previous section appear to bolster those of clinical trials by confirming them in the different setting, such may not always be the case, as other community-based observations may not replicate clinical trial results (eg, spironolactone treatment of heart failure was more problematic in the community setting than in clinical trials[25]). Therefore, it is imperative to evaluate the advantages and disadvantages of clinical trials and other approaches for providing the most reliable and applicable information for patients and healthcare providers.

The intent is not to challenge the role of clinical trials and the educational activities they generate, as these are well-established important and desirable activities. However, they could be complemented by other initiatives aimed at helping to "fill in the gaps" with additional data that appropriately address the community setting. Therefore, alternative means of collecting more representative data are needed and have been called for.[1,6-11,15-18]

Alternative means include the use of subset analyses, targeted clinical trials, observational studies, and registries. It has become commonplace to report subset analyses from large clinical trials. Examples of this include trial results among heart failure subpopulations, defined by ethnicity, sex, comorbidity, and age.[26-30] Whereas this information may be of some value, it remains a subset of the overall clinical trial results and, therefore, has the same limitations as clinical trials. Furthermore, the overall limitations may be magnified in these subset analyses because the sample sizes are

smaller, the question being asked was not prospectively formulated, and randomization may not be balanced for the subset in question. Given these limitations, the results of these subset analyses can be used, at best, to generate hypotheses for testing in subsequent studies and cannot be considered conclusive. Therefore, a new clinical trial targeted at a previously identified subset could be designed. An example of such a targeted clinical trial deriving from subset analyses is the recently announced African American Heart Failure Trial (A-HeFT),[31] designed to prospectively address issues recognized during earlier trials among small numbers of African American patients who appeared to respond differently to treatment.[26-28] However, this approach is still a clinical trial, with the associated limitations of patient and physician selectivity, as well as protocol rigidity.

Observational studies use existing databases to provide large experiences, but are limited by their retrospective nature and the inherent design of the particular database. For example, health claims databases contain coded information, and the accuracy or completeness of coded diagnoses may not meet standards of practice. In addition, much demographic and comorbidity information may be missing. Prescription databases are confined largely to types of drugs prescribed, with limited information about the patient or the indication for the drugs. Therefore, such studies often include inaccuracies of diagnosis and rely on assumptions about the reasons for patient management decisions. These, too, are probably best used for hypothesis generation.

RATIONALE FOR REGISTRIES

Registries are another means of collecting complementary data from the community setting. Compared with a clinical trial, a registry is a database created from a broader source, using flexibly applied means of data collection. Registries may be designed to acquire new information not yet available in any organized fashion. For example, the Coronary Artery Surgery Study[32] registry was begun with the introduction of coronary artery bypass grafting to learn more about the natural history of medically treated coronary artery disease to evaluate the role of the new surgical technology. Registries also provide preliminary data for use in designing clinical trials and comparing patients in a clinical trial with similar patients observed outside the protocol setting.[33,34]

Registries have limitations. They are usually uncontrolled and lack provisions to assure the quality, accuracy, and completeness of data. Furthermore, participation of investigators and patients involves some selection process. Although the β-blocker heart failure registry described herein was designed to simulate the community setting and be less like the clinical trials setting, it had to recruit physicians and patients and ended up with a preponderance of cardiologists. Therefore, these physicians and their patients were selected, at least in part. Nevertheless, this registry may reflect the natural history and management of heart failure in the "real world." That such is the case is suggested by the similarity of the registry's patient characteristics and outcomes to those reported from large databases of community patients with heart failure.[9-19,35-37]

Registries constructed from clinical data are limited by often being retrospective and examining 1 or a few fixed points in time. For example, there is limited information on the natural history of heart failure in the broad population, as the observations derive largely from localized databases examining retrospective data.[9,15] Registries have not been widely used in a prospective manner (as was done in the registry described herein) to collect information longitudinally while the actual data of interest are generated, as is commonly done in a clinical trial. There is a role for prospective collection of data from the community setting to assess the effect of new treatments. To provide a more valid interpretation relative to the clinical trials experience, such community-derived data should include information about the patients and the care providers involved in that setting. Some of these kinds of limitations are exemplified by the Studies of Left Ventricular Dysfunction (SOLVD)[34] multicenter registry, which enrolled patients who were ineligible for the clinical trial and, thus, represented selected patients. In addition, the data were derived from retrospective review, and some registry patients entered a substudy protocol. Finally, the care providers were the same clinical trialists, largely heart failure experts.

That registries are subject to patient and physician selection biases is further exemplified by some recent heart failure registries that have noted important differences between their observations and results from clinical trials. The Management to Improve Survival in Congestive Heart Failure registry noted higher mortality and rehospitalization rates in a community setting, along with reduced use of recommended medications after hospital discharge for heart failure, compared with the reported results of similar clinical trials.[18] The registry patients were predominantly older white women, a marked difference from most clinical trial populations. The Italian Network on Congestive Heart Failure Registry[19] recruited outpatients with heart failure from a community setting and also noted a higher than expected rate of short-term heart failure decompensation, as well as frequent unexplained withdrawal of medications

that are routinely recommended for heart failure. This registry is limited in its generalizability, as the patients were followed up by expert cardiologists in specialized centers and their demographic characteristics were similar to those of patients in clinical trials. The Rochester Epidemiology Project recently compared incidence and survival of heart failure measured a decade apart in the Olmstead County, Minnesota, community.[17] The incidence of heart failure did not change significantly in patient cohorts enrolled in 1981 or 1991, and the survival rate failed to change during that decade of marked advances in heart failure management. The patients in this registry were typical of the community population in that they were older, included more women, and had significant comorbidity, but differed by coming from a predominantly white population of middle to upper socioeconomic class that received much of its healthcare from a prestigious tertiary care provider.

Other registries and observational studies have focused on differences in quality of care and outcomes according to type of healthcare providers and have noted differences in patient characteristics, medication use, and use of procedures among patients managed by cardiologists or primary care physicians, while clinical outcomes have been mixed.[36-38] A limitation of most of these other registries is their use of hospitalized patients to find index cases, rather than recruiting from outpatients, who constitute the much larger and more representative population of heart failure patients. Identifying patients at hospital discharge tends to include a population that is at increased risk of mortality and readmission, whereas most patients with heart failure are ambulatory and have a lower incidence of prior hospitalizations and lower risk of subsequent mortality and hospitalization.[15,18,35] The limitations of this approach have been the subject of recent comment that has called for the establishment of community-based registries for longitudinal observations.[39]

CLINICAL TRIALS VS REGISTRIES

Although the methods of randomized, controlled clinical trials limit the general applicability of their results because of investigator and patient selection biases and adherence to a rigid protocol, they remain the cornerstone for establishing proof of concept and demonstrating efficacy within the populations studied and the particular research environment. It is more difficult and costly to use these same methods to demonstrate comparable results in larger diverse patient populations managed in the usual community care setting. It is not uncommon for new treatments to fail and for new drugs to be recalled by regulatory authorities shortly after their approval and widespread use in the community setting. Regulatory agencies recognize these limitations of small clinical trials and have urged inclusion of broader, more representative patient populations and investigators during the early development of new therapeutic approaches.[40] Therefore, a role for methods other than the randomized, controlled trial may exist.

The heart failure registry experience described herein reinforces the potential value and role of observational studies to assess experience with and outcomes of new treatments outside the clinical trial setting. Like a clinical trial and unlike most registries, the data in this example registry were collected in a longitudinal prospective manner. This should permit interpretation of the results in juxtaposition to those of a clinical trial, with a greater degree of validity than most registry-type data, which are retrospective or point estimates. As already described, registries have limitations. Without an appropriate control group, a registry cannot evaluate efficacy. Therefore, we cautiously interpret the general experience of this β-blocker registry as demonstrating the value of a prospective registry as a tool for collecting data to complement those obtained from more structured clinical trials.

In summary, the relatively small randomized, controlled clinical trial should probably still be used to establish proof of concept and efficacy in the ideal patient population. Other techniques, such as prospective registries, may be more suited to assessing the efficacy and broad applicability of new therapeutic technologies to the real-world community setting. Combining the 2 methods might be a better approach and be more cost effective by limiting the clinical trials (with their high per patient costs) to small numbers of patients and using the low per patient costs of a registry for the large observational studies. The "practical clinical trial" has been suggested as a way of combining these approaches to broaden the diversity of patients and investigators, rendering them more representative of community settings, while maintaining controlled conditions and validity of observations.[1]

CONCLUSIONS

Alternatives to clinical trials, such as registry data, can be used to fill in the gaps left by clinical trials and to provide experience in patient and physician populations that more closely reflects the real world. The registry approach also emphasizes an important role for community physicians as investigators, a role they can fulfill with fewer disruptions to their usual practice than might

be demanded by involvement in clinical trials. A registry can provide community physicians with firsthand experience in using a new treatment modality to confirm or allay their concerns and possible misconceptions about using that new treatment. If the clinical outcomes of a registry parallel the benefits observed in clinical trials, important new therapeutic technologies might be transferred more widely and expeditiously to the community setting. Therefore, the registry experience described herein may serve as an important model for future applications and merit consideration for earlier inclusion in development programs. Successful implementation of different approaches to clinical investigation, such as registries and practical clinical trials, will require government agencies and private industry sectors that support healthcare research to rethink and reprioritize their goals and resource allocation.[1]

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