How to Integrate Multiple Comorbidities in Guideline Development

Article 10 in Integrating and Coordinating Efforts in COPD Guideline Development. An Official ATS/ERS Workshop Report

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***Background*: Professional societies, like many other organizations around the world, have recognized the need to use more rigorous processes to ensure that health care recommendations are informed by the best available research evidence. This is the 10th of a series of 14 articles that were prepared to advise guideline developers in respiratory and other diseases. This article deals with how multiple comorbidities (co-existing chronic conditions) may be more effectively integrated into guidelines.**

***Methods*: In this review we addressed the following topics and questions using chronic obstructive pulmonary disease (COPD) as an example. (*1*) How important are multiple comorbidities for guidelines? (*2*) How have other organizations involved in the development of guidelines for single chronic disease approached the problem of multiple comorbidities? (*3*) What are the implications of multiple comorbidities for pharmacological treatment? (*4*) What are the potential changes induced by multiple comorbidities in guidelines? (*5*) What are the implications of considering a population of older patients with multiple comorbidities in designing clinical trials? Our conclusions are based on available evidence from the published literature, experience from guideline developers, and workshop discussions. We did not attempt to examine all Clinical Practice Guidelines (CPGs) and relevant literature. Instead, we selected CPGs generated by prominent professional organizations and relevant literature published in widely read journals, which are likely to have a high impact on clinical practice.**

***Results and Conclusions*: A widening gap exists between the reality of the care of patients with multiple chronic conditions and the practical clinical recommendations driven by CPGs focused on a single disease, such as COPD. Guideline development panels should aim for multidisciplinary representation, especially when contemplating recommendations for individuals aged *65* years or older (who often have multiple comorbidities), and should evaluate the quality of evidence and the strength of recommendations targeted at this population. A priority area for research should be to assess the effect of multiple concomitant medications and assess how their combined effects are altered by genetic, physiological, disease-related, and other factors. One step that should be implemented immediately would be for existing COPD guidelines to add new sections to address the impact of multiple comorbidities on screening, diagnosis, prevention, and management recommendations. Research should focus on the possible interaction of multiple medications. Furthermore, genetic, physiological, disease-related, and other factors that may influence the directness (applicability) of the evidence for the target population in clinical practice guidelines should be examined.**

INTRODUCTION

Professional societies, like many other organizations around the world, have recognized the need to use more rigorous processes to ensure that health care recommendations are informed by the best available research evidence. The end product of these processes are clinical practice guidelines (CPGs).

CPGs are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances (1). Most CPGs, including guidelines for chronic obstructive pulmonary disease (COPD) (2, 3), collect the available evidence regarding a given disease and provide recommendations for the diagnosis, assessment of severity, and treatment of patients with that disease. However, COPD commonly exists in patients who often have multiple other chronic conditions (hereafter defined as multiple comorbidities) (4, 5), in particular heart failure (6), coronary artery disease (7), hypertension (8, 9), diabetes mellitus (10), metabolic syndrome (11, 12), cancer (13), cachexia (14), skeletal muscle abnormalities (15), depression (16), recurrent pulmonary infections (17, 18), or pulmonary hypertension (19). These multiple comorbidities may influence the clinical manifestations and natural history of COPD, and should be taken into account in the diagnosis, assessment of severity and prognosis, and management of COPD (5, 20–22).

In June 2007 the American Thoracic Society (ATS) and the European Respiratory Society (ERS) convened an international workshop of methodologists and researchers from around the world to coordinate efforts in guideline development using COPD as a model (23). Participants completed the work during the subsequent 4 years to develop a series of recommendations. This is the 10th of a series of 14 articles prepared to advise guideline developers in respiratory and other diseases. The goal of this paper is to describe how patients with multiple comorbidities should be addressed in guideline recommendations, and how issues related to patients with multiple comorbidities can be more effectively integrated in the development of guidelines.

METHODS

The authors of this article addressed the questions listed in Table 1. We did not conduct a systematic review, but we searched PubMed and other databases of guidelines for existing systematic reviews and relevant research on the issue of guidelines,

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TABLE 1. QUESTIONS ADDRESSED REGARDING THE INTEGRATION OF COMORBIDITIES IN GUIDELINE DEVELOPMENT

1. How important are multiple comorbidities for guidelines?
2. How have other organizations involved in the development of guidelines for single chronic disease approached the problem of multiple comorbidities?
3. What are the implications of comorbidities for pharmacological treatment?
4. What are the potential changes induced by comorbidities in guidelines?
5. What are the implications of a population of older patients with comorbidities in designing clinical trials?

including COPD guidelines, and comorbidities. We also consulted references from our own files. Finally, we reviewed guidelines on major chronic diseases from international organizations and examined whether they address the issue of comorbidities in their guidelines. Due to the limited literature, our conclusions are based on a combination of available evidence, the reported practices of organizations involved in developing guidelines, and workshop discussions.

RESULTS

1. How Important Are Multiple Comorbidities for Guidelines?

Multiple comorbidities affect the epidemiology, pathophysiology, and care of COPD, all of which are critical issues usually addressed in clinical guidelines (24). The aging of the population and the decline in the age-specific death rates has led to an increase in the prevalence of multiple comorbidities at advanced ages (25–28). For example, in the United States, one third of Medicare beneficiaries in the 65- to 69-year-old age group and more than one half of those in the 85 or older group have three or more chronic medical conditions (29). Multiple comorbidities increase health care utilization (29–32), mortality (25, 26), worsening of quality of life (33), and disability (34–36).

Risk factors frequently have pleiotropic effects, which themselves have manifold consequences. For example, cigarette smoking is the major risk factor for COPD and is also an important risk factor for cardiovascular, cerebrovascular, and many other common chronic diseases, as well as several types of cancer (37–40). Comorbidities, such as heart failure, hypertension, diabetes mellitus and metabolic syndrome, coronary artery diseases, cachexia, skeletal muscle abnormalities, pulmonary infections, cancer, and pulmonary vascular disease cause variations in the clinical manifestations and natural history of COPD (5). For example, COPD complicates the diagnosis of chronic hear failure (CHF) and is thus associated with unrecognized and untreated CHF in $\geqslant$ 20% of patients (6, 41–43) (Figure 1), and the impaired FEV_1 is a strong biomarker and risk factor of cardiovascular morbidity and mortality (44–46). Patients with COPD often have one or more component of the metabolic syndrome (11), and diabetes mellitus is independently associated with reduced lung function (47).

The presence of both COPD and cardiovascular disease may affect the diagnosis, severity assessment, and clinical manifestations of both conditions (48). For example, the evaluation of dyspnea or fatigue during exercise often depends on what diagnoses the patient already has. If patients have a diagnosis of cardiovascular disease, they are likely to undergo noninvasive cardiac imaging, increasing the likelihood of the diagnosis of heart failure on the basis of left ventricular dysfunction. Alternatively, when patients with stable COPD complain of dyspnea or fatigue during exercise, these symptoms may be attributed to COPD, and cardiac imaging may not be performed, potentially leaving the left ventricular dysfunction undetected (49). In addition, exacerbations of symptoms and hospitalization and mortality of patients with COPD may be caused more by comorbidities than exacerbations of COPD itself (7, 50). As in other diseases, comorbidities markedly affect the natural history of COPD. Patients with COPD mainly die of nonrespiratory diseases, specifically coronary artery, cerebrovascular diseases, and cancer (51–54). Furthermore, the presence of comorbidities such as depression and anxiety may independently affect symptoms and outcomes in COPD (55).

Thus, symptoms of COPD and comorbidities may be overlapping, treatments may interact, underlying pathophysiology may be shared, and the natural history of all conditions may be altered. As a consequence, guidelines for COPD (and other chronic conditions) should include consideration of multiple comorbidities.

2. How Have Other Organizations Involved in the Development of Guidelines for Single Chronic Disease Approached the Problem of Multiple Comorbidities?

Some recent guidelines for COPD acknowledge the importance of considering the role of multiple comorbidities for the diagnosis, clinical manifestations, severity assessment, prognosis, and management of COPD, but acknowledge the lack of evidence and specific guidance for clinicians to do so (56). Unfortunately, the guidelines provide few specific recommendations on how to modify care based on multiple comorbidities (2, 3, 57, 58). The same is true for some examples of recent guidelines for other common chronic illnesses, such as chronic heart failure (59), hypertension (60), and diabetes mellitus (61), which address poorly some comorbidities, including COPD, one at a time, but do not address the coexistence of multiple comorbidities at the same time. Cox and colleagues analyzed guidelines for five common chronic conditions (diabetes, heart failure, hypertension, osteoporosis, and stroke) in regard to the evidence used to support them and how they inform providers about patients of advanced old age with multiple chronic conditions (62). They evaluated 14 guidelines for age-specific recommendations, particularly for the identification or inclusion of frail older individuals, individuals older than 80 years of age, and individuals with multiple chronic conditions. They summarized their finding by stating that there is very low representation of individuals with advanced old age within guidelines and the studies upon which these guidelines are based. They, therefore, questioned the applicability of current chronic disease guidelines to older individuals.

Mutasingwa and colleagues conducted a content analysis of published Canadian guidelines for diabetes, dyslipidemia, dementia, congestive heart failure, depression, osteoporosis, hypertension, gastroesophageal reflux disease, chronic obstructive pulmonary disease, and osteoarthritis (63). They focused on the presence or absence of four key indicators of applicability of guidelines to elderly patients with multiple comorbidities (e.g., mentioning of older adults or people with comorbidities, time needed to treat to benefit in the context of life expectancy, and barriers to

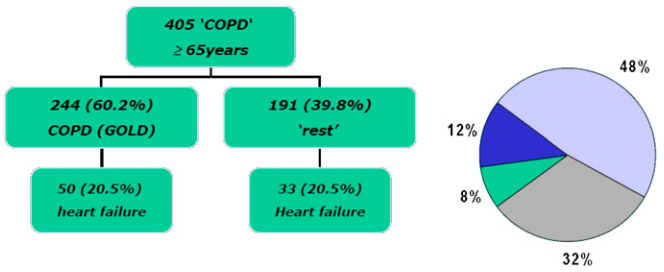

Figure 1. Prevalence of heart failure in stable chronic obstructive pulmonary disease (COPD) (subjects aged 65 yr or more). Data taken from Reference 49). *Pie chart*: *green*, HF only; *dark blue*, HF + COPD; *light blue*, COPD only; *gray*, negative for both HF and COPD.

implementation of the guidelines). The investigators observed that although most guidelines discuss the elderly population, few adequately address issues related to elderly patients with comorbidities (63).

There are some examples of collaborative guideline development that may serve as a model for future work to address the care of people with multiple comorbidities (23, 64, 65). The European Society of Cardiology has joined with other groups to develop recommendations for cardiovascular disease prevention in clinical practice (66). The American Geriatrics Society/California HealthCare Foundation has developed a guideline for the care of the older patient with diabetes mellitus, which extensively considers the impact of multiple comorbidities (65). The group selected six chronic conditions common in people with diabetes mellitus and reviewed guidelines and literature on each topic, developed evidence tables that summarized the data from randomized controlled trials (RCTs) on each topic, and modified existing or developed new guidelines. The panel found limited data specific to older adults with diabetes mellitus for most of the topic areas. For some areas, there were data from studies of older persons. For other areas, there were data for persons of younger ages with diabetes mellitus and the panel judged that it was reasonable to extrapolate the findings to older adults with diabetes mellitus. Recommendations were formulated as described in the two examples in Table 2. The approach chosen by the American Geriatrics Society/California HealthCare Foundation appears explicit and transparent. However, a clearer consideration for patients' values and preferences and the need for patient and clinician prioritization of the problems that should be addressed would further enhance the implementability of these guidelines as well as their relevance to everyday clinical practice. Table 3 suggests strategies for considering multiple comorbidities in the development of CPGs and patient involvement in their implementation in clinical practice. We believe that all chronic disease guidelines should have a separate section on comorbidities providing a summary of basic recommendations on diagnosis, assessment of severity, and treatment of each comorbid condition that can either be derived from other high-quality guidelines or developed *de novo*.

3. What Are the Implications of Multiple Comorbidities for Pharmacological Treatment?

Decisions about pharmacologic treatment represent a key area in the development of CPGs where the consideration of the impact of multiple comorbidities is crucial. A primary focus on management of a single disease may inadvertently lead to undertreatment, overtreatment, or inappropriate treatment of a patient whose health care needs may change based on the presence of multiple comorbidities (67). In particular, excess medication administration can result from adding treatments for the same condition when other causes are not considered and when there is a lack of response to therapy. This, in turn, can have unintended consequence of attempts to prevent or treat individual diseases by increasing costs, compromise adherence, and augment the risk of adverse drug events (58). Randomized clinical trials are frequently explicitly designed to exclude patients with comorbidities that may interfere with the detection of therapeutic efficacy, or which theoretically may increase the risk of adverse events (68, 69). Drugs may therefore have unanticipated effects on patients with other illnesses.

The problem of adverse side effects of medicines in patients with COPD and comorbidities is well appreciated by clinicians. For instance, systemic steroids are recommended for the treatment of exacerbations of COPD, but increase the risk of hyperglycemia in patients with COPD and diabetes mellitus (70), and may worsen osteoporosis. Conversely, β-blockers are recommended for the treatment of chronic heart failure (59, 60), but can exacerbate respiratory symptoms in patients with COPD who also have asthma (2). Bronchodilators, both β-agonists and anticholinergics, seem effective and safe in patients with COPD alone, but may increase adverse events if COPD is associated with heart failure (71) or arrhythmias.

Pharmaceutical agents can also have pleiotropic effects. Angiotensin-converting enzyme (ACE) inhibition, the cornerstone of treatment of CHF and hypertension (59, 72), may reduce mortality and morbidity in COPD (73) and improve respiratory muscle strength in patients with CHF (74). Statins, used primarily as lipid-lowering agents in the treatment of metabolic syndrome, have antiinflammatory properties that could affect co-morbidities of metabolic syndrome (e.g., COPD, CHF, and vascular diseases) (73, 75, 76).

A major reason for the lack of guidelines that address the care of people with multiple comorbidities is that the evidence on which to base the guidelines is usually very limited and indirect. RCTs are usually designed and performed for single diseases, have narrow inclusion criteria (58, 67, 69), and the populations examined frequently exclude chronic complex patients (69). More fundamentally, clinical trials are typically designed to answer a single question regarding therapeutic efficacy for a medication treating an index condition. The use of an agent with both positive and negative effects on co-existing chronic illnesses implies trade-offs that depend on the relative effects of the agent on each of the co-existing illnesses, the relative severity of the illnesses in a given patient, and patient preferences. Such questions may be difficult to answer in the context of a clinical trial. As a result, those developing clinical practice guidelines must make judgments about the degree to which the research evidence applies to patients with multiple comorbidities. Strategies can be used to account for the possible effect modification and interaction of different pharmacological agents. They can demonstrate that either the effects will differ in the population for whom the recommendation is intended from that in whom the evidence is obtained, or that there is evidence of an interaction between different interventions that would change the benefit–downside profile compared with when the interventions are administered alone. When developing recommendations for patients with COPD and multiple comorbidities, it would be ideal to evaluate the effects of the drugs in the population for whom the recommendation is intended rather than relying solely on evidence

TABLE 2. EXAMPLE RECOMMENDATIONS FROM GUIDELINES THAT EXPLICITLY CONSIDERED MULTIPLE COMORBIDITIES

1. "The older adult who has diabetes mellitus and hypertension should be offered pharmacological and behavioral interventions to lower blood pressure within 3 months if systolic blood pressure is 140 to 160 mm Hg or diastolic blood pressure is 90 to 100 mm Hg or within 1 month if blood pressure is greater than 160/100 mm Hg (IIIB). There are no data on the optimal timing for initiation of treatment for hypertension, but expert opinion supports the recommendation that the severity of blood pressure elevation should influence the urgency of initiating therapy. (Source guideline: 11)".
2. The older adult who has diabetes mellitus is at increased risk for major depression and should be screened for depression during the initial evaluation period (first 3 months) and if there is any unexplained decline in clinical status. (IIA)

Note: recommendations included a detailed statement about the underlying evidence that followed the recommendation. Reprinted by permission from Reference 65.

TABLE 3. A GUIDE FOR DEVELOPMENT OF MULTIPLE COMORBIDITY CLINICAL PRACTICE GUIDELINES AND PATIENT INVOLVEMENT IN DEVELOPMENT OR APPLICATION (NOTE THAT THE EXAMPLES SHOULD NOT BE USED FOR DECISION MAKING)

Step	How	Example for COPD
Define all problems for a given patient	Ask patients (and list all problems) or review the literature on importance of problems for patients	Define which of the following is of primary concern for patients: dyspnea, depression, swelling of legs
Which outcome is of greatest importance to a patient with multiple co-morbidity (e.g., reducing hospitalizations, improving dyspnea)	Use tools to elicit values and preferences for that (e.g., visual analog tools, ranking exercises)	Feelsing thermometer, simple ranking techniques comparing dyspnea with fatigue and hospitalizations (described in detail)
Define possible options to intervene	Literature search (focus on systematic reviews), experts input on what might work	LABA, diuretics, beta-blockers, antidepressants (is the patient ready to accept few interventions only?)
Evaluate whether benefits or downsides (including harms) differ across populations (in particular those with different multi-morbidity)	Evaluate subgroup effects/heterogeneity across populations: use data from individual patient meta-analysis, observational studies, etc. Did trials include subgroups? (use checklists of whether subgroup effects are credible). Is there evidence that biology differs? Make judgment about directness of the evidence	LABAs may be worse in patient with dyspnea from COPD and CHF. Treatment of dyspnea leads to improvement of depression. Beta-blockers (although the evidence is not conclusive) with slightly more harm in patients with COPD and CHF
Evaluate greatest net benefit across populations (harms, downsides, values, and preference weighted) based on evidence profiles and present to panel making recommendations and patients	Systematically judge the expected benefits against the potential downsides after considering various interventions. Explain to patients	Beta-blockers with greatest net benefit in the population of interest. Treatment of depression may be of second largest net benefit. LABA and diuretic net benefit may be smaller than net benefit from beta-blockers—therefore patients having to decide for two of four medications may choose beta-blockers and antidepressants

Definition of abbreviations: CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; LABA = long-acting β-agonists.

obtained from healthier patients. In the latter case, the evidence is less direct compared with evidence that directly supports recommendations, and it would influence the confidence in how the obtained effects relate to population of interest.

4. What Are the Potential Changes Induced by Multiple Comorbidities in Guidelines?

A critical underlying question is: How should physicians make treatment recommendations for people with multiple comorbidities, particularly if they are elderly? Realistic patient-oriented guidance requires a paradigm that incorporates these judgments (58), since clinical decision-making in such patients requires the estimation of the often subtle balance of the benefits and risks (including adverse treatment-related events) that will determine whether there are net benefits or net harms. This evaluation will frequently involve considerable uncertainty, and requires estimation of a baseline risk over a given time period. The values and preferences patients place on the treatment options and the outcomes too have to be incorporated into the decisions. These values and preferences are influenced by factors such as treatment burden and the individual's definition of quality of life. Guidelines for COPD and other diseases need to support decision making by acknowledging these factors in this complex clinical context if they are to be useful to clinicians.

The GRADE system provides a useful framework for grading both the quality of the evidence behind a recommendation and considering how strong the recommendation should be (77). Even when otherwise "high-quality" randomized studies are available, the evidence will frequently be indirect for the multimorbid population and, therefore, the quality of the evidence may be downgraded. Thus, the general effect of multiple comorbidities may be to increase the likelihood of a close or an uncertain balance between desirable and undesirable effects (risks and benefits), thus weakening the strength of the recommendations for this population.

To address these issues, comorbidities could be considered in all disease guidelines by first explicitly discussing whether patients with the most common comorbidities were included in the disease-specific trials. However, as Kravitz and colleagues have described, the determination as to whether the results of a study apply to an individual patient is not whether the patient would meet the trial inclusion criteria but whether he or she is sufficiently like, or exchangeable to, the average patient in the trial to make meaningful the resulting estimate of the average treatment effect (78). A heterogeneous sample does not eliminate concern about heterogeneity of treatment effects, because the dispersion of effects across subgroups may still be large, and analytic methods must avoid erroneous conclusions about subgroup effects (79, 80). Recommendations should be based on evidence that comes from the target population for which the guideline is intended, allowing targeting of specific recommendations to different groups within this population (58). Guidelines could be more useful if there was greater clarity in identifying exactly which of the many possible multiple morbidities were considered for which of the several recommendations within one guideline. Review of the evidence in layers considering both people with and without multiple comorbidities, as well as people at different ages, should be considered since the heterogeneity of health status regardless of the comorbidities increases with older ages. However, age alone is seldom useful in determining treatment. An older person without significant comorbid disease burden may be more likely to benefit from a therapy than a younger person with significant disease burden, or vice versa.

Second, the absolute risk reduction from a therapy for a person with one or more comorbidities must be considered, recognizing that a person with multiple comorbidities may be at either higher or lower absolute risk than the "average" person. The specific comorbidities may need to be discussed individually as the effect of the multiple comorbidities depends on the specific combinations of conditions in question. Is it known whether the relative benefit of the therapy increases or decreases in people with each combination of the multiple comorbidities? In some cases, people with multiple comorbidities may be at higher risk of a bad outcome and therefore more likely to benefit, but in other cases the risk of harm or the competing risks of dying of something else may negate or reverse the positive effects of a therapy aimed at COPD (81, 82). Thus, appropriate methods

to analyze data from heterogeneous populations are needed to understand possible variations in net treatment benefit (83).

Third, the guideline should specify the actual outcomes of each therapy, whether desired or undesired (84). If a clinician is working to apply a guideline to an individual, and is weighing and discussing the potential benefits and downsides of a therapy, it is important to have it clearly stated what the expected outcomes are (i.e., improvement in function, relief of symptoms, prevention of a stroke) (Table 3). This is not always explicit in current guidelines (58).

Fourth, the average and extremes of the length of therapy necessary to achieve this degree of risk reduction or symptom improvement should be presented. The concept of time to benefit from a therapy is essential for patients with competing risks who may have shortened life expectancy (85). The concept of "payoff time" may provide a method of tailoring guidelines to individual patients, and this will be influenced by individuals' values and preferences (83).

Fifth, guidelines should address interactions that are common or important given the prevalence of specific comorbidities. These potential interactions between a comorbidity and drugs for COPD, or between a drug for COPD and a drug for a comorbidity, or between COPD and a drug for a comorbidity, or between nonpharmacologic therapeutic recommendations, require explication.

A critical question for a patient with COPD and one or more comorbidities is what are the patient's goals or priorities for care and treatment? All of the above questions are necessary to consider in determining priorities in an individual with COPD. There is an increasing body of evidence that clinicians do not always prioritize correctly even when there is a reasonable body of evidence to guide these complex decisions (86, 87). In practice, prioritization for an individual patient requires syntheses of evidence within or across conditions. However, another critical piece must come from the patient (Table 3).

Guidelines should describe that patient preferences should always be included in discussions of goals and the selection of management decisions and that the patient's preference should be incorporated in decisions. Guidelines should provide simple summaries of risk and benefits of therapies in language that users of guidelines can communicate with patients. Recognition that patient preferences affect treatment regimens throughout the course of the disease and long before end-of-life discussions is essential. Clinicians need to know the information that they would communicate with patients such as "this therapy reduces the risk of a hospitalization for COPD of the next year from y to z for people like you" or "this therapy made 50% of people who only had COPD (without other conditions contributing to shortness of breath like you have) feel less short of breath when they walked." For example, decision analysis of the risks and benefits of warfarin use discussed with older persons with atrial fibrillation led to poor agreement with recommendations derived from guidelines, suggesting that even with excellent information and collaborative decision-making, patients may not always choose to follow guideline recommendations (88). There is often little information in guidelines on how to discuss risks, benefits in patient-friendly language to elicit preferences (89).

Feasibility, which is primarily driven by available resources, of implementing guideline recommendations must also be considered closely in the context of patients with multiple comorbidities. One facet of feasibility is medication regimen complexity (58). Methods for simplification of COPD regimens should be presented as well as discussion of the trade-offs of simplification (i.e., once per day tiotropium is more effective but also more expensive than the ipratropium 4 times per day).

Building on this, discussion of patient preferences should include the burdens of therapies and other barriers to adherence—for example, taking diuretics may make getting out and exercising or socializing difficult. Finally, how guidelines should best address comorbidities requires further study and initiatives to address this issue are underway (90).

5. What Are the Implications of a Population of Older Patients with Comorbidities in Designing Clinical Trials?

The patients in clinical trials that are the foundation of our current evidence base do not adequately reflect the true population of people with any chronic disease in terms of burden of multiple comorbidities (69). Similar to trials for other chronic conditions, older patients and patients with major comorbidities are specifically excluded from most clinical trials conducted in patients with COPD (91–94). Fortunately, the number of trials with explicit age exclusions for older patients has decreased. However, the percent of older patients in trials does not yet approach the percent of the overall population who are older (69, 95, 96). While age exclusions have decreased, there is some evidence to suggest that exclusions for comorbidities have increased. For example, the number of heart failure trials excluding participants with specific comorbidities increased from 1985 to 1999, with more than half of such trials excluding people with major hepatic, renal, or hematologic comorbidities (68). Again, two recent large and long COPD trials (i.e., HEALTH TORCH and UPLIFT) excluded patients with cardiovascular comorbidity (93, 94) and, thus, developing recommendations for patients with COPD and cardiovascular disease requires careful consideration of the directness of the evidence (*see* Table 3).

Exclusion and inclusion criteria are less important than who is the "average" patient in a trial; if there are few exclusion criteria, but if few people with comorbidities are actually enrolled, the results are still of questionable relevance to patients with multiple comorbidities (78). Another critical issue is that synthesizing trial results with limited generalizability to the true population with the condition may produce inappropriate guidelines for prevalent subgroups seen in practice (97) due to heterogeneity of treatment effects, defined as the "magnitude of the variation of individual treatment effects across a population" (78). A clinical trial that includes a more heterogeneous population may also see more heterogeneity of treatment effects. Average effects are not always useful, as they can represent harm to some patients, little benefit to patients who were at low risk to begin with, and a great deal of benefit to others.

Strategies for managing and understanding heterogeneity of treatment effects have been described (79, 80, 97, 98). These

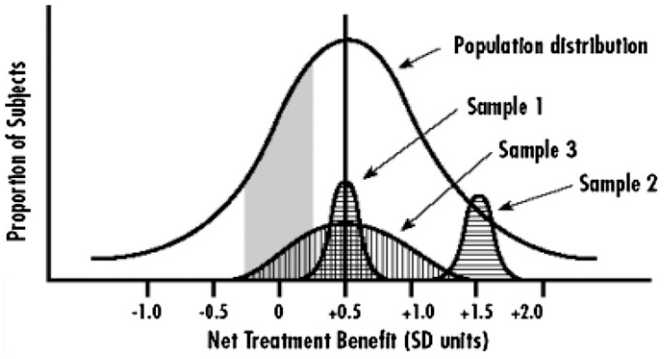

Figure 2. Sample 1: centered, but fails to reflect the diversity of the population. Sample 2: individuals who much more benefit from treatment than do average members of the population. Sample 3: broadly representative of the population in terms of risk, responsiveness, and vulnerability. Reprinted by permission from Reference 78.

include pretrial identification of risk groups; definition of *a priori* hypotheses; hypotheses about the direction of subgroup effects, including those at risk for poor outcomes; redesign of trials to allow for adequate power for pre-planned key subgroup analyses and analyses of heterogeneity of treatment effects; and learning from longitudinal observational studies to inform generalizability (Figure 2).

CONCLUSIONS

Few guidelines have explicitly considered patients with multiple comorbidities (58). Detailed methods for developing recommendations for patients with multiple comorbidities are lacking. Implementing single disease guidelines presents important challenges to the clinician treating not the average clinical trial patient, but the population of patients with COPD who frequently have multiple comorbidities. We used COPD as an example for a chronic disease in this and other manuscripts in this series, and we focused mainly on nonrespiratory comorbidities. The overlap between COPD and respiratory comorbidities such as lung carcinoma, bronchiectasis, and asthma has been extensively discussed in the literature reported in COPD guidelines (54). The issues raised in this article provide a basis for a framework (Table 3) that will facilitate the integration of multiple comorbidities in the formulation and application of recommendations. We believe that it is time to tackle this issue in more depth. A critical step is the use of broader enrollment criteria and appropriate methods in randomized trials to ensure that the clinical research evidence directly addresses the populations for whom clinicians provide care in their clinical practice.

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