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Future Research Directions for Multimorbidity involving Cardiovascular Diseases

Marcel E. Salive, MD, MPH

National Institute on Aging, NIH; Bethesda, MD, Address: 7201 Wisconsin Avenue, Suite 3c307, MSC 9205, Bethesda, MD 20892-9205

Synopsis

Multimorbidity, defined as the co-occurrence of two or more chronic conditions, increases with age and may be found in about 2/3 of older adults in population studies, commonly including a variety of cardiovascular risk factors and chronic diseases. This article offers a research agenda for cardiovascular disease from a patient-centered multimorbidity perspective. Definitional issues remain for multimorbidity, along with high interest in understanding the inter-relationships between aging, diseases, treatments, and organ dysfunction in the development and progression of multimorbidity. Clinical trials, practice-based and population-based observational studies, and linkages of “big data” can play a role in improving health outcomes among persons with multimorbidity.

Keywords

Multimorbidity; aging; chronic disease; multiple morbidities

Introduction

Multimorbidity, or multiple chronic conditions (MCC) is defined as the coexistence of two or more chronic conditions, and has been observed in about 2/3 of older adults in many population studies, making it the “most common chronic condition”. 1 Although MCC lacks a standardized definition in some respects, considerable research has been published demonstrating its substantial human burden in terms of symptoms, medications, treatment costs, and quality of life. 2 Multimorbidity is increasing faster than any single disease, and is increasing across all age groups. 3 No core list of chronic conditions has been widely accepted to define MCC, however, most population-based studies of the topic are dominated by persons with hypertension, hyperlipidemia, coronary artery disease and other cardiovascular diseases (CVD). This paper will advance a set of future research directions

Corresponding Author: Marcel E. Salive, msalive@msn.com, Marcel.salive@nih.gov.

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for multimorbidity involving cardiovascular diseases, using an interdisciplinary patient-centered (*not disease-centered*) approach, and with the intent of moving the field forward by translating evidence into policy and practice.

Geriatricians and others have previously developed research agendas related to multimorbidity, in an effort to broaden the focus from single diseases or organ systems. 4, 5, 6 Subsequently the Department of Health and Human Services released its Strategic Framework on Multiple Chronic Conditions in 2010. While a major focus has been on the Strategic Framework's Goal 4, “Facilitate research to fill knowledge gaps about, and interventions and systems to benefit, individuals with multiple chronic conditions”, substantial work has addressed the other goals: 1) foster health system change; 2) empower individuals and 3) equip clinicians. 6 In the spirit of a cycle approach to research agenda setting, this paper will approach cardiovascular disease but from a patient-centered multimorbidity perspective. With this broad scope, it must be recognized that any set of research directions is subjective and not definitive. Available sources that were examined include prior published research agenda, recent meetings and grant portfolio analysis. A research agenda focused on cardiovascular disease in the context of multimorbidity can address broad scientific issues that are important to the populace.

Framework for multimorbidity and CVD

This paper will employ the prominent frameworks for multimorbidity. While some studies of multimorbidity have analyzed several diseases and conditions at once, other studies have evaluated interactions between just two or three conditions (dyads and triads), for example hypertension and diabetes. Another approach is the co-morbidity paradigm, where research focuses on an index condition and its co-existing conditions (e.g., comorbidities of coronary artery disease). 7 Among comorbid conditions, concordant conditions have similar underlying pathophysiology and may be more the focus of the same disease management plans, for example diabetes is considered concordant with hypertension, coronary artery disease and peripheral vascular disease. 8 Atherosclerotic vascular disease is another salient example, which manifests in the body systems as cerebrovascular, cardiovascular or peripheral artery disease, although they commonly co-occur. Conversely, discordant conditions are not directly related in either pathology or management, such as discordance of coronary artery disease with low back pain, prostate cancer, and arthritis. Another important concept among the multimorbid conditions is that one condition may be clinically dominant such as an end-stage disease or one which is severely symptomatic, such as Class IV congestive heart failure. Finally, some research uses the true multimorbidity approach, where the diseases are considered equally without ranking, and the focus is on the impact on the patient.

The frameworks themselves raise several researchable questions. While a widely accepted definition of multimorbidity is two or more chronic conditions, this could achieve wider consensus, and alternatives such as 3 or more conditions could be examined and rejected. Which conditions should be included on a universal list of chronic conditions? Should obesity, hyperlipidemia, urinary incontinence, and other geriatric syndromes (cognitive impairment, delirium) be on that list? 10 How should atherosclerosis be included? Should

cardiovascular diseases be grouped with stroke? How to optimize the framework for research on combinations of CVD and MCC? Which dyads and triads including CVD are most in need of new research?

Much of the focus of basic science is on identifying underlying causes of multimorbid diseases and understanding the role of aging (Figure 1). Aging, as well as certain etiological factors, may lead to loss of reserve and organ dysfunction. Some of the causes interact with aging, and the diseases as they progress may feedback onto the causal factors. A substantial research agenda includes methods development to distinguish the effects of aging from factors that cause disease or make it progress or increase in severity. 9

Within the multimorbid patient, there may be disease-disease interactions such as the hypertrophic remodeling of the right ventricle (cor pulmonale) that may accompany a variety of chronic respiratory diseases. Other disease-disease interactions may be identified by systematically examining the molecular mechanisms underlying complex diseases. This search includes whether the pathways of one disease may perturb those of another disease, resulting in shared clinical and pathobiological characteristics.

Most chronic diseases have available drug interventions, which give rise to concerns about the potential for interactions. Serious drug adverse events might be viewed as a type of drug-disease interaction, and overall such events cause considerable mortality and health care utilization. Persons with multimorbidity may be at risk of another drug-disease interaction, sometimes referred to as “therapeutic competition,” arising when the treatment of one disease adversely affects (competes with) another coexisting condition. 10 Drugs recommended for one condition can be contraindicated or recommended to be avoided in the presence of the other condition. Two well-publicized examples of therapeutic competition are the effects of a COX-2 inhibitor for arthritis on heart disease and rosiglitazone for diabetes increasing heart failure symptoms. Disease-treatment interaction may also arise for therapeutic procedures or subsequent to device implantations. Within the multimorbid person, diseases may progress, become more severe and lead to both disease-specific and universal (patient-centered) outcomes. Universal outcomes are those that occur across multiple conditions and are less disease-specific, such as self-rated health, symptom burden, functional status, and quality of life.

A proposed research agenda follows and is listed in the Key Points and Table 1.

Basic Science and Discovery

Among the most frequent co-occurring chronic conditions, the elucidation of common underlying pathways is a high priority that might lead to broad clinical applications. The interdisciplinary field of geroscience aims to understand the relationship between aging biology and age-related diseases. Aging is a universally experienced risk factor underlying the development of most chronic diseases and can also accelerate disease occurrence at the levels of the cell, tissue, organ and entire human. Characterize the chronic diseases more fully and enable personalization of treatments. For most diseases, an intermediate or pre-clinical phenotype is either not identified or well-defined. Can subtypes of a chronic disease be identified, and does this enable identification of additional concordant chronic

conditions? What are the common, or underlying mechanisms or metabolic pathways that are involved? What interventions can be developed and tested to alter the pathogenesis?

Mechanistic studies need to be systematically focused on multimorbid phenotypes, so that disease mechanisms are better understood and to help identify molecular basis of the pathobiological relationships between diseases. 11 Interventions can be developed for these underlying mechanisms, and studied for broader impact on multiple disease outcomes. Animal models that pertain to combinations of chronic conditions have been targeted, but with limited success. Better animal models are needed for multimorbidity, otherwise many of these complex studies will need to be conducted on humans.

Clinical Trials

Many chronic disease interventions have been evaluated in randomized clinical trials for safety, efficacy and sometimes effectiveness. At present, the paradigm for therapeutics development focuses on one disease at a time. Important aspects of interventional clinical trials related to multimorbidity and CVD include increasing the enrollment of multimorbid persons in such trials, expanding the use of universal outcome measures, and developing trials that target multmorbidity itself. Selected head-to-head comparative effectiveness and safety trials in persons with prevalent dyad or triad disease combinations that include CVD are a high priority.

Applying the multimorbidity framework to clinical research, and in particular RCTs can be challenging. Few studies, and in particular clinical trials of cardiovascular interventions, explicitly enroll multimorbid persons; rather, they may exclude many specific chronic conditions, most of which increase with age. Clinical trials should ascertain comorbid disease, enroll multimorbid persons to study applicable interventions, and examine patient-centered outcomes relevant to health benefits and harms.

Meaningful outcomes are required for clinical trials in persons with multimorbidity. The persistence and progression of diseases and courses of treatments affect health status in multiple dimensions such as physical and mental health, pain and other symptoms, therefore well-validated universal outcome measures across diseases are needed for research and practice. A minimum senior data set might include such outcomes as general health; pain; fatigue; and physical health, mental health, and social role function, and measured gait speed. 12

Multimorbidity itself can be a focus for intervention trials, in selected instances. However, the choice of which conditions to include in a composite endpoint of multiple chronic conditions must be made very strategically. This approach is fraught with risks, not least of which is that it differs from the single condition treatment approach that has traditionally been adopted by regulatory agencies. In particular, a strong rationale for the likelihood that a specific intervention could prevent or treat several major chronic conditions would be required. Furthermore, parsimony in choosing conditions and similarity of the perceived importance of the conditions may be considered in developing a composite. Nevertheless, some candidates may emerge, and a large successful trial using a multimorbidity outcome

of, for example, cardiovascular disease, cancer and dementia could develop strong evidence that would potentially have a major public health impact.

Practice-based Research

There is a great need for research based in clinical practice involving the care of persons with multimorbidity and cardiovascular diseases. Common dyads and triads are particularly well-suited for this type of research. By eliciting and addressing patient goals of care, the treatment of complex patients with cardiovascular and other chronic illnesses can optimize the person-centered outcomes. Coordinating the care of the multiple chronic conditions can be done in various ways, and optimizing those approaches in practice would achieve significant health benefits. It is well-known that persons with MCC are among the highest users of medical resources, yet the treatment of multimorbid patients is fraught with complexity with issues such as polypharmacy and the limitations of practice guidelines that have not adequately considered potential disease-drug interactions. Clinical decision support tools that address the complex issues of combinations could be developed and tested in a variety of care settings. Interventions that encourage de-prescribing of certain dangerous, ineffective or non-recommended drugs could be developed and tested.

Self-management can be transformed into a holistic multimorbidity management tool that avoids disease-specific approach and instead addresses prevention and patient goals.

Much of this work will also involve development and testing new models of health care, since these patients are the most difficult to manage. An over-arching and important issue is how to deal with complexity and optimize care coordination? Ultimately this approach involves the transformation of specialty and primary care.

Population-based research

While RCTs remain the gold standard for comparative studies, exclusions as well as resource limitations compel continued use of observational studies for many comparative-effectiveness research questions. Well-known susceptibility to bias, as well as confounding by indication, give impetus to consideration of several key factors in interpreting the results of observational drug studies, including biologic plausibility, magnitude of differences, new-user design, validity of endpoints, and replication of findings. 13 New outcome measures may be developed for big-data surveillance of drug-drug and drug-disease interactions and adverse effects.

One novel incremental approach to addressing gaps in the observational data on multimorbidity involves increasing data linkage along with selective new data collection (Fig 2). Building blocks for this approach include existing CVD registries, which may be populated with persons who have a specific cardiovascular disease, procedure, implant or surgical procedure. They should be enhanced by adopting a standardized approach to phenotyping the chronic conditions. Using 2 or more such registries might enable inclusions of multiple treatment options for a specific condition (e.g., surgical and medical management of a common underlying condition). The linkage to Medicare administrative claims data may enable ascertainment of a variety of pharmacological, rehabilitation and other services potentially involved in the treatment. Direct data collection will be required

for ascertainment of patient reported outcomes such as symptoms and quality of life. This infrastructure is beginning to be applied to studies of multimorbid persons, but its extension and generalization as part of the “Big Data” era may produce substantial advances in knowledge. In particular, the ascertainment of multimorbidity can be cross-validated to reduce the persistent misclassification and biases that may exist in previous research.

Methods development is also needed in the pursuit of multimorbidity research. Alternative statistical methods could be developed for evaluating these programs and interventions that involve greater complexity. Better methods are needed to study decision-making under uncertainty and also to incorporate variation in patient preferences.

Guidelines

Few clinical guidelines offer an approach to managing the problems of multimorbidity, rather they focus on a single disease. However, this problem cannot be addressed in isolation since it reflects a paucity of applicable research/evidence. Therefore, acknowledging multimorbidity is just a first step, before it can be included more fully in the guideline development process. 14 Specific combinations such as common dyads or triads may require tailored guidance. However, common discordant conditions may raise a serious challenge, particularly when the relationship between the two conditions is not fully established or understood, such as with coexisting depression and CVD. Ultimately, guideline change will be driven by the entire body of relevant clinical research evidence enabled by linkage of high quality data, incorporating at least relevant drug-disease interactions and the evaluation of risks and benefits for persons with complex combinations of conditions. 15

Quality Measurement

With the stated intention of some payors to transition to a payment system that pays for value and outcomes rather than service delivery, comes a need for measures of value and outcomes that are applicable to multimorbidity. Universal outcome measures for multimorbidity might be suitable as quality measures if they are shown to be valid, responsive, feasible and can be applied with few exclusions in clinical practice. 12 Most quality measures at present are disease-specific and process-oriented. Quality measure development of tools suitable for multimorbidity that areNOT disease-specific will need to rest on a foundation of evidence. Eventually, the improvement of meaningful health outcome measures will drive health care and innovation.

Conclusions

Future research on multimorbidity would be facilitated through development of a consensus definition of multiple chronic conditions that can be employed in linked medical records. In addition, etiologic studies of multimorbidity should expand to include co-occurrence of cardiovascular, other physical and mental health conditions. Methodologic development should be extended for observational studies of comparative treatment effectiveness among multimorbid older adults with CVDand complex treatment regimens. Clinical trial evidence guiding treatment of complex, older adults can be improved by eliminating upper age limits for study inclusion, by reducing the use of eligibility criteria that disproportionately affect

multimorbid older patients and by evaluating outcomes that are highly relevant to older individuals. Pragmatic trials of treatment strategies for multimorbidity that employ universal health outcomes as primary or secondary endpoints may be particularly fruitful.

Research infrastructure grants can be an effective platform for observational studies of multimorbidity, polypharmacy and comparative effectiveness, and for pragmatic interventional trials. Many funding agencies have expressed an interest in this research including foundations, the Agency for Healthcare Research and Quality, several institutes of the National Institutes of Health, and the Patient-Centered Outcomes Research Institute. The potential for public health impacts of a program of research on multimorbidity cannot be overstated.

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Key Points

- A research agenda focused on cardiovascular disease in the context of multimorbidity (two or more chronic conditions) can address broad scientific issues that are important to the populace.
- Systematic understanding of the molecular mechanisms underlying complex and potentially interacting chronic diseases can be developed to improve strategies for treatment and prevention.
- Clinical trials should ascertain comorbid disease, enroll multimorbid persons to study applicable interventions, and examine patient-centered outcomes relevant to health benefits and harms.
- By eliciting and addressing patient goals of care, the treatment of complex patients with cardiovascular and other chronic illnesses can optimize the person-centered outcomes.
- Guideline development must systematically approach the most common and salient disease combinations, and in the case of an absence of evidence, outline high-priority research questions.

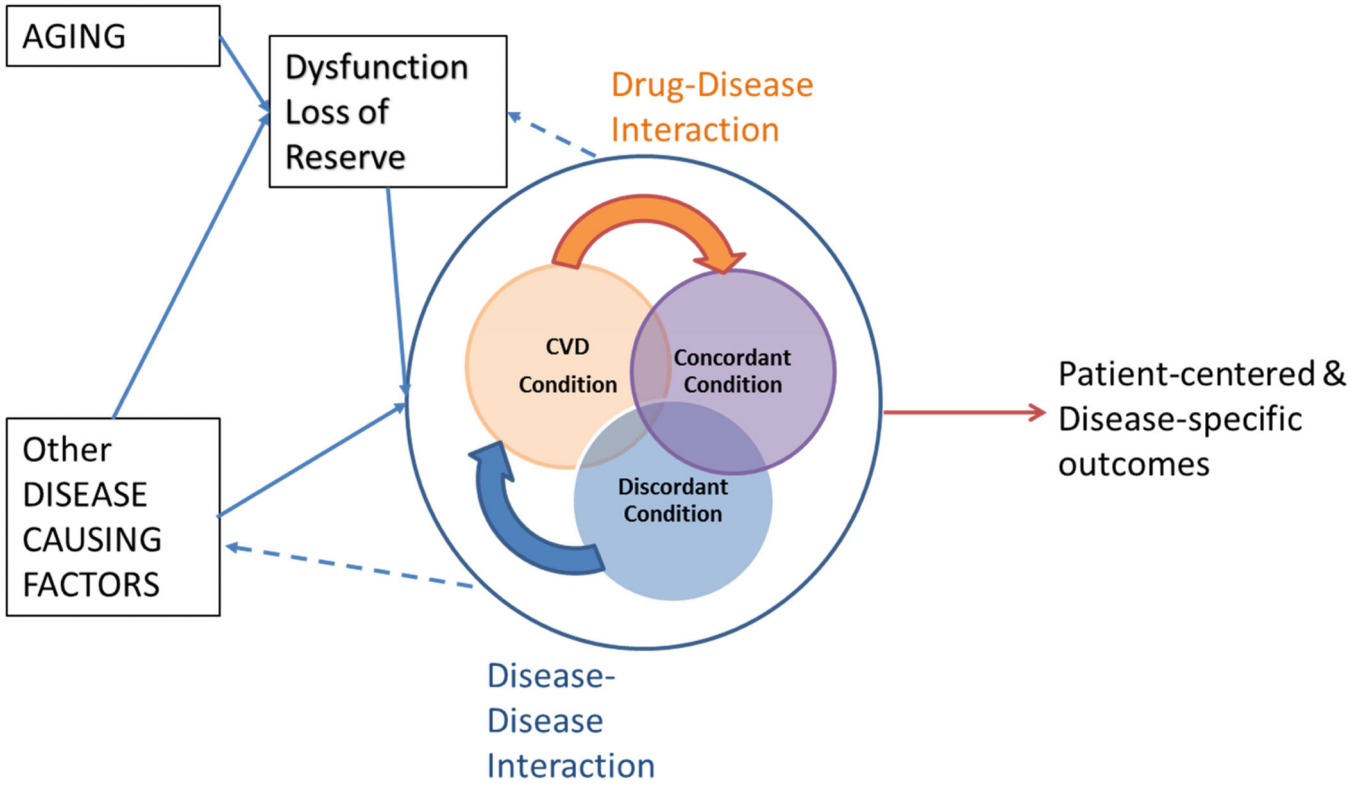

Figure 1.
Model of interaction of aging, underlying causes, modifiers and chronic conditions in multimorbidity.

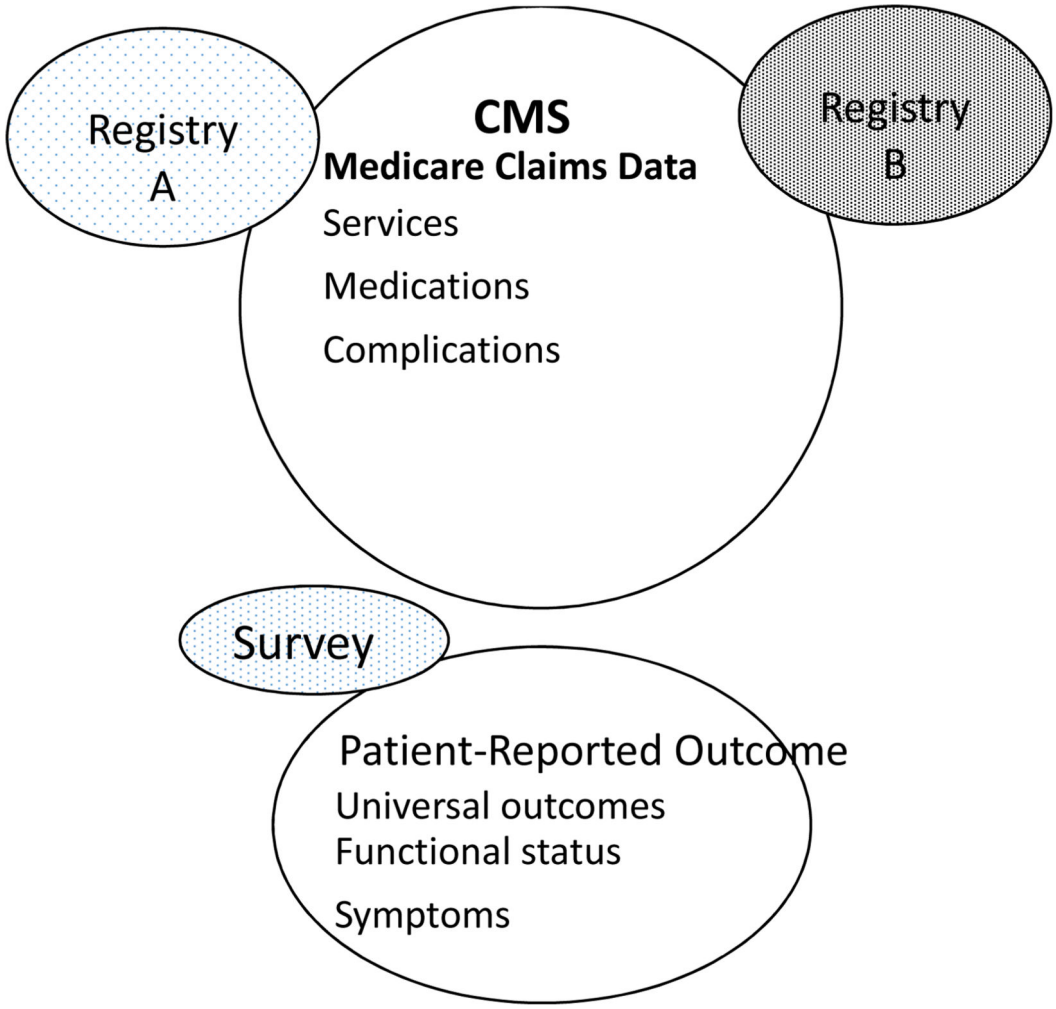

Figure 2.
Proposed approach to improve multimorbidity study linking multiple data sources.

Table 1

Research directions for multimorbidity that includes cardiovascular disease

Overarching topics	Develop research programs on high priority dyads and triads of conditions Obtain consensus on multimorbidity definition and which CVD conditions to routinely include
Basic Science	Examine biological pathways and systems for underlying causes of specific combinations of chronic conditions Develop and evaluate therapeutic approaches for dyads based on mechanistic studies Develop methods to distinguish effects of aging from factors causing disease and increasing its severity Elucidate basic science of behavior to improve self-management of chronic disease
Clinical Trials	Reduce exclusions based on comorbid chronic disease for most trials Evaluate tailored interventions for older persons with multimorbidity and CVD Increase use of universal outcomes in CVD clinical trials Develop and test multimorbidity outcome that could be applied to prevention trials
Practice/Implementation	Develop a minimal phenotyping approach to chronic conditions that can be used in longitudinal studies and linkable electronic health records Develop methods to identify patient goals and incorporate them into care of persons with multimorbidity and CVD, including use in shared decision-making tools Develop and validate risk prediction instruments that include outcomes of importance to patients, including comorbid conditions as predictors Develop and evaluate self-management approaches to multimorbidity for dyads and triads
Guidelines and Quality Measures	Translate research on high-priority dyads and triads into CVD guidelines Evaluate guideline dissemination approaches on CVD guidelines that have incorporated the dyad and triad information in primary care Develop approach for guidelines to deal with conditions that are discordant to CVD such as depression and chronic pain Develop and refine quality measures for persons with MCC and CVD that can be used for quality improvement programs in primary and specialty outpatient care