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# Current guidelines poorly address multimorbidity: pilot of the interaction matrix method

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## Abstract

**Objectives:** To develop a framework to identify and classify interactions within and among treatments and conditions and to test this framework with guidelines on chronic heart failure (CHF) and its frequent comorbidity.

**Study Design and Setting:** Text analysis of evidence-based clinical practice guidelines on CHF and 18 conditions co-occurring in ≥5% of CHF patients (2−4 guidelines per disease). We extracted data on interactions between CHF and comorbidity and key recommendations on diagnostic and therapeutic management. From a subset of data, we derived 13 subcategories within disease−disease (Di-Di-I), disease−drug (Di-D-I), drug−drug interactions (DDI) and synergistic treatments. We classified the interactions and tested the interrater reliability, refined the framework, and agreed on the matrix of interactions.

**Results:** We included 48 guidelines; two-thirds provided information about comorbidity. In total, we identified $N = 247$ interactions (on average, 14 per comorbidity): 68 were Di-Di-I, 115 were Di-D-I, 12 were DDI, and 52 were synergisms. All 18 comorbidities contributed at least one interaction.

**Conclusion:** The interaction matrix provides a structure to present different types of interactions between an index disease and comorbidity. Guideline developers may consider the matrix to support clinical decision making in multimorbidity. Further research is needed to show its relevance to improve guidelines and health outcomes. 

*Keywords:* Heart failure [MeSH]; Multimorbidity; Comorbidity [MeSH]; Practice guideline [MeSH]; Interactions; Drug interactions [MeSH]

## 1. Introduction

Clinical practice guidelines have shown to have a considerable potential to improve health care in chronic conditions, such as chronic heart failure (CHF) [1,2]. Despite this fact, most of the current disease-oriented guidelines do not (appropriately) address relevant co- and multi-morbidity [3,4]. Boyd et al. showed that an uncritical application of the recommendations of various guidelines on different conditions in caring for patients with multimorbidity—that is, the co-occurrence of two or more acute or chronic conditions [5]—is not feasible and may actually have undesirable effects, such as interactions within and among treatments and conditions [6]. Physicians report that handling interactions in the management of patients with multimorbidity in primary care is cumbersome [7]. Therefore, (primary care) physicians and health policy makers emphasize the importance of the development of guidelines covering the needs of clinical decision making in ''real'' patients, that is, patients with multiple conditions and complex health care needs [8−12].

Patients suffering from CHF may serve as a paramount example: they are usually older, 95% of the cases have at least one and often even multiple co-occurring conditions [13−15]. Moreover, CHF is a multisystemic disorder in itself, and evidence-based treatment recommendations lead to the prescription of five or more long-term medications in symptomatic patients, that is, polypharmacy [16]. This pharmacologic

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**What is new?**

- This article provides a systematic approach to address co- and multi-morbidity in disease-oriented guidelines.
- This article suggests a classification of interactions in multimorbidity, that is, within and among multiple treatments and conditions, and shows its feasibility in chronic heart failure.
- The application of the classification to a chronic disease and its common co-occurring conditions results in an interaction matrix presenting omissions, matters of caution, safe, synergistic principles, and gray zones of clinical management.
- An interaction matrix may support the assessment and weighing up of potential benefits and risks in the clinical management of patients with multiple conditions.
- An interaction matrix may serve as an additional tool to assist the development of clinical decision support in patients with multiple conditions in disease-oriented guidelines.

treatment has a considerable potential for drug−disease and drug−drug interactions in case of any further comorbidity [17]. Well-known examples of disease−drug interactions are nonsteroidal anti-inflammatory drugs (NSAIDs) to relief from pain, which may worsen heart failure [18], and cardioselective β-blockers, which are indicated in heart failure but contraindicated in asthma [19].

Our aim was to develop and test a framework to help guideline developers and others identify and classify important interactions between the target disease and comorbid diseases and their treatments. We aimed to test this framework within CHF and its frequent noncardiac comorbidity by means of a crosscheck of clinical practice guidelines.

## 2. Methods

### 2.1. Data sources

#### 2.1.1. Comorbidity

To make the selection of relevant comorbid diseases, we relied on a study assessing a large number of physician-diagnosed medical conditions that are relevant to the course of CHF [14]. Braunstein et al. reported 18 noncardiac conditions with a prevalence of at least 5% [14], and for some aggregated conditions, further specification was necessary (in parenthesis): asthma, benign prostatic hyperplasia, chronic back disorders (low back pain), chronic kidney disease, COPD and bronchiectasis, dementia, depression, diabetes mellitus, hypercholesterolemia, hypertension, lower respiratory diseases (LRD, including lower respiratory tract infection), ocular disorders (ocular hypertension/glaucoma), osteoarthritis, osteoporosis, peripheral and visceral atherosclerosis, and thyroid disorders (hyper- and hypo-thyroidism).

#### 2.1.2. Guidelines

We then searched for clinical practice guidelines addressing either CHF or one of these conditions at Guidelines International Network (G-I-N) Library and at the Web sites of established guideline developing organizations (National Institute for Health and Care Excellence [NICE], Scottish Intercollegiate Guidelines Network, and the German Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften [Association of the Scientific Medical Societies in Germany]). With the aim to include a criterion-based sample for the purpose of the pilot study, we selected two to four guidelines per disease (if available) which should be:

1. evidence-based (ie, evidence levels and/or a grading were reported in the majority of recommendations with a clear link to supporting evidence),
2. comprehensive (ie, recommendations were covering a broad range of clinical decisions within the management of the target disease),
3. actual (before the date of expiry),
4. addressing the primary care management of the disease, and
5. developed by an established organization with high methodological standards.

If more than four guidelines were available, we selected primarily the most recent and the most comprehensive European guidelines.

### 2.2. Data extraction, development of framework, and matrix

Two authors (C.M. and H.K.) extracted the following data from the included guidelines: interactions between CHF (or cardiovascular diseases) and the 18 selected comorbid diseases and key recommendations on diagnostic and therapeutic management of the disease under concern, including recommended drugs and drugs to be avoided.

From a subsample of data, we derived categories of interactions. First, interactions were classified into the three accepted main categories: disease−disease (Di-Di-I), disease−drug (Di-D-I), and drug−drug interactions (DDI) [12]. Second, subcategories were formed taking into consideration the direction (CHF−comorbidity and comorbidity−CHF) and the effects of the interaction (symptoms, safety, and potential harm). Third, two additional main categories were formed: synergistic interactions to indicate a treatment that participates in an effect of synergy on CHF and comorbidity (either potentially beneficial or harmful)