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Upper Gastrointestinal Symptoms and Cardiovascular Disease

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1. Introduction

Cardiovascular disease, primarily encompassing coronary heart disease, hypertensive heart disease, heart failure, and stroke, is the number one cause of death globally, with 17.3 million dying from such causes in 2008 and a projected 23.6 million dying from cardiovascular disease in 2030 [1]. Cardiovascular disease affects 1 in every 3 Americans, or an estimated 83.6 million people (myocardial infarction, 7.6 million; angina pectoris, 7.8 million; heart failure, 5.1 million; and stroke of any kind, 6.8 million; high blood pressure, 77.9 million) [2]. Heart disease and stroke results in over 500,000 and 160,000 deaths, respectively, each year in the United States; giving rise to an enormous annual economic burden exceeding \$312 billion in both direct and indirect costs [1,2].

Upper gastrointestinal (or dyspeptic) symptoms, often sub-classified as ulcer-like (localized epigastric pain or nocturnal/fasting pain), gastroesophageal-like (heartburn or regurgitation) or dysmotility-like dyspepsia (postprandial fullness, early satiety, diffuse epigastric pain, belching or abdominal distention) are also highly prevalent worldwide with an average 3-month prevalence rate across an international sample of survey respondents of about 28%, but with higher rates in some countries such as the United States (41.8%) [3] and lower rates in others (Japan's rate=9.4%). Clinically-relevant upper gastrointestinal symptoms have been found to result in high healthcare utilization [4,5]; as noted in one study [4] which found 20% of affected patients visited a physician's office during the 3-months prior to being surveyed, 2% were hospitalized, nearly half used an over-the-counter medication and 27% were prescribed at least one medication to address their symptoms. Upper gastrointestinal symptoms have

also been associated with significant costs due to lost work productivity [4,5], with those suffering symptoms having an 85% (95% confidence interval, 40%-145%) increased odds of work absenteeism [5], 27% reporting at least one day of reduced or no productivity over a 3-month period, and 89% of this subset of people reported more than one day affected [4]. In addition to these direct and indirect costs, increased intangible costs (pain and suffering) are also an important repercussion of upper gastrointestinal symptoms [6], with these symptoms shown to be associated with significantly impaired wellbeing and patients' ability to perform activities of daily life (subjects reporting relevant upper gastrointestinal symptoms had significantly worse Psychological General Well-Being Index (PGWBI) and Interference with Daily Life Index (IDLI) scores compared with those reporting no or non-relevant symptoms (PGWBI score 65.24 versus 77.91, $p<0.0001$; IDLI score 75.85 versus 98.57, $p<0.0001$). Both cardiovascular disease and upper gastrointestinal symptoms are common diagnoses in daily practice. According to the American Academy of Family Physicians, numerous diagnosis codes for both cardiovascular disease and upper gastrointestinal symptoms are among the most frequently billed for [7].

In addition, cardiovascular and upper gastrointestinal disorders are among the top 20 leading diagnoses for direct health expenditures in the United States [2]. In 2008, approximately \$95.6 billion dollars were spent treating heart conditions and \$27.2 billion were spent treating upper gastrointestinal disorders, making these two disease states the first and twelfth most costly diagnoses, respectively, for direct healthcare expenditures. Since cardiovascular disease and upper gastrointestinal symptoms are both common conditions, some overlap in the occurrence of these conditions would naturally be expected.

Diagnosis description	Diagnosis code (ICD-9-CM)
<i>Cardiovascular disease</i>	
Atrial fibrillation	427.31
Chronic ischemic heart disease, unspec.	414.9
Heart failure, congestive, unspec.	428.0
Hypertension, benign	401.1
Hypertension, unspecified	401.9
Chest pain, unspec.	786.50
<i>Upper gastrointestinal symptoms</i>	
Gastroenteritis, noninfectious, unspec.	558.9
Gastroesophageal reflux, no esophagitis	530.81
Nausea w/ vomiting	787.01

Table 1. International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Cardiovascular Disease and Upper Gastrointestinal Symptoms Designated in the Top 100 According to the 'Family Practice Management Short List' [reference 7]

Beyond both having relatively high frequencies in daily practice and large economic burdens, there are clinical data supporting the hypothesis that upper gastrointestinal symptoms are more prevalent in patients with cardiovascular disease. Previous studies have found upper gastrointestinal symptoms to occur as much as twice as often [8] in patients suffering from a cardiovascular disease [9-13], and moreover, some upper gastrointestinal disorder may increase patients' risk for cardiovascular disease [14-17].

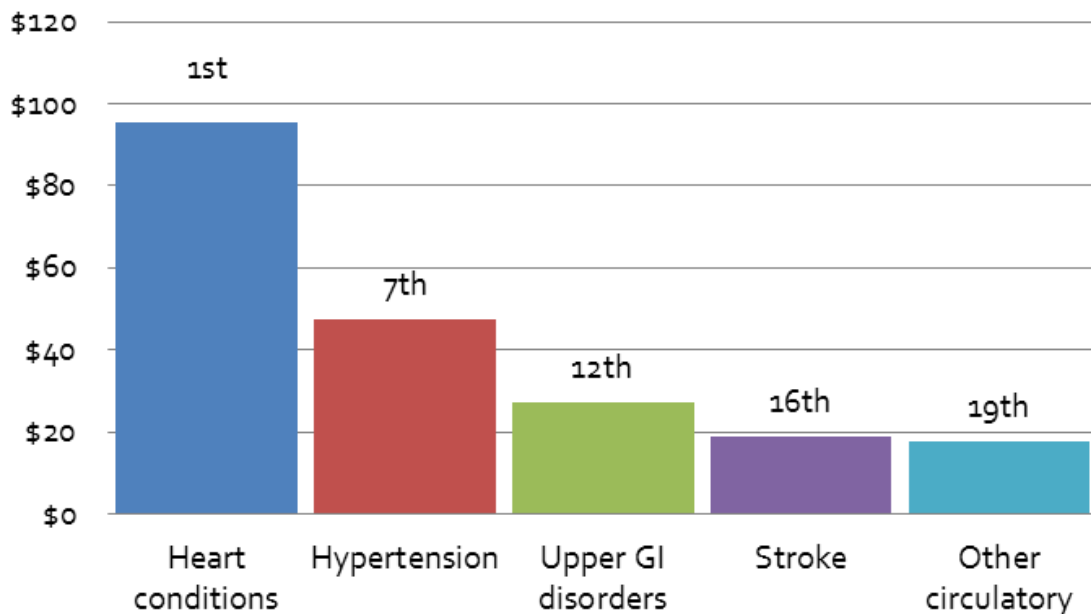


Figure 1. Cardiovascular Disease and Upper Gastrointestinal Symptoms on the List of 20 Leading Diagnoses for Direct Healthcare Expenditures (adapted from reference 2) Bars depicts the cost each diagnosis in 2008 US\$, while the labels above the bars provides each diagnosis' ranking in direct healthcare expenditures.

The finding of higher prevalence rates of upper gastrointestinal symptoms in patients with cardiovascular disease may exist for a number of reasons. First, there are a host of mutual risk factors for developing both cardiovascular disease and upper gastrointestinal symptoms [18-37]. Next, patients experiencing both health problems often complain of similar or overlapping symptomatology, potentially resulting in the more frequent surveillance and diagnosis of both [38]. Related to this, some studies have suggested that common means of investigating upper gastrointestinal symptom origin can aggravate some cardiovascular diseases or induce cardiovascular symptoms [39,40]. Finally, polypharmacy with drugs used to manage cardiovascular diseases can cause upper gastrointestinal symptoms [8,41-46] resulting in decreased adherence to their medications, and a perhaps initiating a cycle of recurrence/worsening of cardiovascular disease. Moreover, some drugs to treat upper gastrointestinal symptoms may increase cardiovascular disease risk either directly or through drug-drug interactions.

The aim of this chapter is to provide a detailed discussion of the evidence suggesting and supporting an increased risk of upper gastrointestinal symptoms in populations suffering from cardiovascular disease.

2. Evidence supporting the link between cardiovascular disease and upper gastrointestinal symptoms

At least a half dozen published studies [8-13] have demonstrated a link between cardiovascular diseases and an increased risk of upper gastrointestinal symptoms. Three of these studies have assessed the association of upper gastrointestinal symptoms with general cardiovascular diagnosis. A recent study created two cohorts of patients derived from health insurance claims data from the Human Capital Management Services research database over a four year period (2001-2004)[9]. The cohorts were based upon the presence or absence of functional dyspepsia diagnosis codes, with the control cohort (n=83,450) being matched to the functional dyspepsia cohort (n=1,669) using a propensity score that included variables such as age, sex, marital status, salary, among others. This study demonstrated that employees with functional dyspepsia were 1.8-fold more likely to suffer from circulatory system disease (prevalence=39.19% in those with functional dyspepsia versus 22.37% in the control group; p<0.05).

Study, year (N=)	Study Description	Key Finding
Brook 2012 (N=275,875)	Retrospective database analysis of paid health insurance claims within the Human Capital Management Services research database (USA); 275,875 eligible employees, 1,669 with functional dyspepsia diagnosis codes	Higher prevalence of circulatory system disease in those with functional dyspepsia versus controls (ratio=1.8:1; prevalence=39.19% in those with functional dyspepsia versus 22.37% in the control group; p<0.05)
Stanghellini 1999 (N=5,581)	Respondents of the Domestic/International Gastroenterology Surveillance Study which surveyed urban, adult populations from 10 countries representing seven geographic areas (Canada, the USA, Switzerland, The Netherlands, Italy, Japan and the Nordic countries) using a study-specific symptom checklist; prevalence rate of upper gastrointestinal symptoms=28%	Higher odds of cardiovascular condition (OR=2.0), myocardial/endocardial/pericardial/valve condition (OR=2.7) or vascular (extracardiac) condition (OR=2.8) in patients with UGIS diagnosed by a doctor Higher odds of self-reported cardiovascular symptoms (OR=1.5), or myocardial/endocardial/pericardial/valve symptoms (OR=4.4) over previous three months in patients with UGIS
Wallander 2007 (N=17,949)	Analysis UK General Practice Research Database to identify patients with new onset dyspepsia in 1996; overall incidence=15.3	Higher odds of chest pain (OR: 2.4, 95%CI 2.1-2.7) or angina (OR=1.5, 95%CI=1.2-1.8) comorbidity in dyspepsia cohort in the year prior to index date than control cohort

Study, year (N=)	Study Description	Key Finding
	(95%CI 15.0-15.6) per 1000 person-years (n=6,913)	Higher odds of having first time diagnosis of chest pain (OR=2.3, 95%CI=2.0-2.8) or angina (OR=2.7, 95%CI=1.8-4.0) in dyspepsia group in the year after index date than in control cohort
Lohr 1986 (N=4,962)	Respondents completing a questionnaire enrolled in the Rand Health Insurance Experiment from six sites (Dayton, Ohio; Seattle, Washington; Fitchburg, Massachusetts; Franklin County, Massachusetts; Charleston, South Carolina; and Georgetown County, South Carolina); prevalence rate of ulcer-like symptoms per 100 (aged 18-61 years) men=3.8 and women=3.8	Congestive heart failure and angina were associated with a 3.6-fold (p<0.001) and 2.9-fold (p<0.05) higher odds of ulcer-like symptoms
LaMori 2012 (N=1,297)	Respondents to the 2009 National Health and Wellness Survey, a nationwide (USA) self-administered internet-based questionnaire; prevalence rate of dyspepsia=34%	Dyspepsia more likely among patients with higher stroke risk (CHADS ₂ ≥2, OR=1.15) Patients reporting dyspepsia in addition to AF had higher mean CHADS ₂ scores (1.9 vs. 1.4, p<0.05)
Laliberte 2012 (N=413,168)	Retrospective database study of Thomson Reuters MarketScan data from 2005 and 2009 to quantify the incidence of dyspeptic events in patients with atrial fibrillation; median follow-up of 563 days	Incidence rate of dyspepsia was found to be 14.7 per 100-patients years
Pasini 1989 (N=NR)	Italian patients affected with congestive heart failure and ischemic heart disease studied to ascertain relation between dyspeptic syndrome and acute cardiac disorders	Data showed alterations of motility in esophagus, stomach, duodenum in every patient and lesions of gastric mucous membrane in more than half

AF=atrial fibrillation; FD=Functional dyspepsia; HLD=hyperlipidemia; HTN=hypertension; NA=not applicable; NR=not reported; OR=odds ratio; UK=United Kingdom; UGIS=upper gastrointestinal symptoms; USA=United States of America

Table 2. Studies Assessing Upper Gastrointestinal Symptoms in Patients with Cardiovascular Disease

A second study, the large Domestic/International Gastroenterology Surveillance Study [8] looked to investigate any association between upper gastrointestinal symptoms (gastroesophageal-, ulcer- or dysmotility-like) and lifestyle factors (including comorbidities) in a large sample of patients experiencing dyspepsia in the prior 3-months. A sample of urban, adult populations from seven geographic areas (Canada, United States, Switzerland, the Netherlands, Italy, Japan and the Nordic countries) was obtained by door-to-door or telephone recruitment. Subjects were divided into groups depending on whether gastrointestinal

symptoms were reported and were analyzed for the association with comorbid conditions. In total, 5,581 subjects were recruited, with 1,566 (28%) reporting relevant upper gastrointestinal symptoms. In the previous three months, subjects reporting gastrointestinal symptoms self-reported more general cardiovascular (odds ratio= 1.5) or vascular myocardial/endocardial/pericardial and valve (odds ratio=4.4) symptoms or illnesses. Subjects with upper gastrointestinal symptoms also had increased prevalence of clinician-diagnosed cardiovascular (odds ratio=2.0) or myocardial/endocardial/pericardial and valve (odds ratio=2.7) conditions.

Two more large studies [10,11] have reported on a link between the prevalence of upper gastrointestinal symptoms with angina and chest pain. The first, a cross-sectional study of 6,913 patients aged 20-79 with new diagnoses of dyspepsia and 11,036 age- and sex-matched control patients from the United Kingdom-based General Practice Research Database, demonstrated dyspeptic patients are at increased odds of having a diagnosis for chest pain (odds ratio=2.4, 95% confidence interval=2.1-2.7) or angina (odds ratio=1.5, 95% confidence interval=1.2-1.8) within the previous year. In addition, dyspeptic patients are also more likely to receiving receive a first time diagnosis for chest pain (odds ratio=2.3, 95% confidence interval=2.0-2.8) or angina (odds ratio=2.7, 95% confidence interval=1.8-4.0) [10]. In an older study of 4,962 patients aged 18-61 who took part in the Rand Health Insurance Experiment, a decade-long randomized controlled trial of the effects of alternative methods of financing health care services, about 30% had one chronic illness, with an additional 16% having 2 or more. Ulcer-like symptoms, defined by a previous diagnosis along with taking antacids daily, frequent episodes of stomach pain relieved by milk, occurring one-half hour after eating or at night, was significantly associated with angina ($p<0.05$) and congestive heart failure ($p<0.001$) [11].

A single study sought to assess the prevalence of dyspepsia among patients with atrial fibrillation [12]. The population ($n=1,297$) included a nationwide sample of American adults (from the 2009 National Health and Wellness Survey) with atrial fibrillation divided into two groups: those reporting dyspepsia (defined as any of the following: ulcers, abdominal bloating, abdominal pain, gastroesophageal disease or heartburn) and those who did not. Of these atrial fibrillation patients, 41% reported a diagnosis of a gastrointestinal condition while 34% reported a diagnosis of dyspepsia. Patients with dyspepsia were associated with a significantly higher mean CHADS₂ score (1.9 vs. 1.4, $p<0.05$). Of note, while the CHADS₂ score was developed as a tool to determine atrial fibrillation patients' risk for stroke, in this case, it can also serve as a marker of the presence of cardiovascular diseases since 2 of 5 CHADS₂ criteria (eg, stroke and congestive heart failure) are in fact cardiovascular diseases and the remaining 3 criteria (eg, age, hypertension, diabetes) are potent risk factors for cardiovascular disease.

A retrospective database study sought to assess the risk of dyspepsia among patients with atrial fibrillation [13]. Analysis of insurance claims from the MarketScan® database from 2005-2009 was conducted. The population ($n=413,168$) included patients ≥ 18 years at the date of first atrial fibrillation diagnosis, with 180 days of continuous insurance coverage prior to the index atrial fibrillation diagnosis, and no gastrointestinal event within 180 days of the index atrial fibrillation diagnosis. The risk of dyspepsia was assessed with incidence rates (IRs; new dyspepsia case per patient years of observation). During a mean follow-up of 563 days, the IR

of dyspepsia for patients with atrial fibrillation was 14.7 events per 100 patient years. At baseline, 62% of patients (n=257,357) had at least one medication which may cause gastrointestinal tolerability issues. The authors conclude that atrial fibrillation was associated with a 40% risk of developing a gastrointestinal event, which was predominantly dyspepsia.

Finally in a small case series evaluating the relationship between dyspepsia and congestive heart disease or ischemic heart disease in Italian patients, data showed alterations of motility in the esophagus, stomach and duodenum in every cardiovascular disease patient evaluated and lesions of the gastric mucous membrane in more than half [14].

In addition to the aforementioned data suggesting upper gastrointestinal symptoms are more prevalent with patients with cardiovascular diseases; a body of literature suggesting upper gastrointestinal symptoms may in fact induce cardiovascular disease has begun to take shape [15-18]. In 2003, the first signal that gastro esophageal-like symptoms or disease could be linked to the development of atrial fibrillation was published [15]. Clinicians in Australia looked at 18 patients with concomitant diagnoses of lone paroxysmal atrial fibrillation and gastroesophageal reflux disease and noted that after treatment with a proton pump inhibitor to treat the upper gastrointestinal symptoms, 14 of 18 had a decrease or disappearance of at least one paroxysmal atrial fibrillation symptom.

Since that time, 3 observational studies [16-18] have more thoroughly evaluated this link. In a cohort study of 163,627 patients receiving care from the United States Army National Capitol Area Military Healthcare System between 2001 and 2007 (5% had atrial fibrillation and 29% had gastroesophageal-like symptoms), gastroesophageal symptoms were associated with an increased risk of atrial fibrillation, even after adjusting for age, sex, race and atherosclerotic risk factors (relative risk=1.19, 95% confidence interval=1.13-1.25) or further adjustment for ischemic heart disease, cardiomyopathy, atrial septal defect and being status post-cardiac bypass surgery (relative risk=1.08, 95% confidence interval=1.02-1.13) [16].

The second study [17] similarly sought to assess the relationship between gastroesophageal reflux disease and atrial fibrillation; and the researchers assessed the risk for atrial fibrillation over a follow-up period of greater than 11 years. A self-report survey was sent to 5,288 patients aged 25-74 over the 6 year period of 1988-1994. Of these patients, 741 developed atrial fibrillation. Contrary to the previous study, an inverse relationship with observed between gastroesophageal reflux disease symptoms and atrial fibrillation risk (hazard ratio=0.81, 95% confidence interval=0.68-0.96). However, the frequency of symptoms in those with gastroesophageal reflux (none, some, weekly, daily) was associated with an increased hazard of atrial fibrillation ($p < 0.01$ for overall association); with daily symptoms associated with the highest hazard (hazard ratio=1.30, 95% Confidence interval=0.98-1.57) of developing atrial fibrillation compared to no gastroesophageal symptoms ($p = 0.07$ unadjusted and $p > 0.2$ after adjustment for confounders). The researchers cite an increase in medical attention in those experiencing gastroesophageal reflux as a possible explanation for the lack of association between the presence of symptoms and atrial fibrillation; hypothesizing that extra physician visits resulting from gastroesophageal symptoms resulted in early and more frequent identification and treatment of known atrial fibrillation risk factors, as well as a higher utilization of proton pump

Study, year (N=)	Study Description	Key Finding
Weigl 2003 (N=18)	Endoscopic reports of 640 Austrian patients searched for diagnosis of lone PAF and mention of reflux esophagitis; 18 patients invited to assess the effect of PPI therapy for GERD on paroxysmal AF-related symptoms	PPI therapy led to a decrease or disappearance of at least one PAF-related symptom in 14 of 18 patients.
Kunz 2009 (N=163,627)	Cross-sectional cohort study of adults in the United States Army National Capitol Area Military Healthcare System database; 7,992 patients with diagnosis of AF; 47,845 with diagnosis of GERD	GERD associated with increased risk of AF (RR=1.39, 95%CI=1.33-1.45; aRR=1.19, 95%CI=1.13-1.25#; aRR=1.08, 95%CI=1.02-1.13†)
Bunch 2009 (N=5,288)	Longitudinal survey study of Olmstead County, Minnesota residents to assess long-term risk of AF with symptomatic GERD; 2,577 (49%) reported GERD; 741 (14%) developed AF over 11.4 year follow-up period	The presence of GERD was associated with a decreased risk of AF (HR=0.81, 95%CI=0.68-0.96) The frequency of symptoms in those with GERD was associated with an increased hazard of AF (p<0.01); with daily symptoms associated with the highest risk (HR=1.30, 95% CI=0.98-1.57; p=0.07) compared to none.
Shimazu 2011 (N=188)	Cross-sectional survey study of Japanese patients completing screening questionnaire for GERD based upon frequency of 12 common symptoms to evaluate the relationship between AF and GERD; 46% with AF	AF was associated with prevalence of GERD (F-scale score≥8 points) (p<0.001 upon multivariate analysis). The dyspeptic sub-score (2.05±0.29 vs. 0.94±0.12, p=0.018) and the total F-scale score (3.98±0.51 vs. 2.12±0.21, p=0.019) of AF patients were significantly greater than those in normal sinus rhythm.

*Widely used questionnaire in Japan to screen for gastroesophageal reflux disease based upon frequency of 12 common symptoms

#Adjusted for age, sex, race, known atherosclerotic risk factors (hypertension, diabetes, hyperlipidemia, and tobacco use)

†Adjusted for strong correlates of AF: ischemic heart disease, cardiomyopathy, atrial septal defect, status post coronary bypass surgery

AF= atrial fibrillation; aRR= adjusted relative risk; GERD= gastroesophageal reflux disorder; HR= hazard ratio; PAF= paroxysmal atrial fibrillation; PPI= proton pump inhibitor; RR= relative risk; USA= United States of America

Table 3. Relationship Between Atrial Fibrillation and Gastroesophageal-Like Symptoms

inhibitors (although the researchers did not have data medication use to test this hypothesis). Finally, the most recently published study assessed the relationship between atrial fibrillation and gastroesophageal reflux disease in 188 Japanese patients between 28-91 years of age [18]. Patients' gastroesophageal reflux disease status was classified using the F-scale, a questionnaire specifically designed to screen for gastroesophageal reflux disease. Almost half of

enrolled patients had a diagnosis of atrial fibrillation ($n = 86$), and while hypertension, dyslipidemia or coronary artery disease were not associated with the prevalence of symptomatic gastroesophageal reflux disease (defined as a total F-scale ≥ 8 points) upon multivariate analysis, atrial fibrillation did show a significant correlation with gastroesophageal reflux disease ($p < 0.001$). In addition, both the dyspeptic sub-score ($p = 0.018$) and the total F-scale score ($p = 0.019$) of atrial fibrillation patients were significantly greater than those in normal sinus rhythm.

Recognizing patients with both cardiovascular diseases and upper gastrointestinal conditions is an important step in their medical care. As demonstrated in available evidence, the links between the conditions are strong, and can impact therapeutic decisions.

3. Shared risk factors

The World Health Organization, World Heart Federation [1] and the American Heart Association [3] each agree on a set of risk factors for the development of cardiovascular diseases. These risk factors include smoking, being overweight or obese, living a sedentary lifestyle, and poor diet, as well as having pre-existing diagnoses of high cholesterol, hypertension and diabetes.

In addition to significantly contributing to the risk of developing cardiovascular disease, these same risk factors have also been found in epidemiologic studies to be associated with an increased risk of reporting upper gastrointestinal symptoms. These risk factors are highly prevalent both worldwide and in the United States [1,3].

Below we discuss the mechanism behind, and studies supporting, the association between these risk factors and increased rates of upper gastrointestinal symptoms.

3.1. Current smoking

Over a billion people worldwide are thought to be current smokers. It is estimated that nearly six million people die from tobacco-related deaths annually, and by 2030, this number is projected to surpass 8 million. Smoking is the underlying cause of about 10% of cardiovascular disease [1] and has been consistently found to be a strong and independent risk factor for myocardial infarction and sudden death [2]. Similar findings have been observed with cerebrovascular disease and smoking; with smokers having a 2 to 4 times increased risk of stroke compared with nonsmokers [2]. Consequently, it is not surprising that a large number of studies support the beneficial cardiovascular consequences of smoking cessation [1].

It is theorized that tobacco smoking/use induces upper gastrointestinal symptoms through its effects on the gastric mucosa [19]. The nicotine in tobacco likely causes mucosal injury by augmenting acid and pepsin release, causing duodenogastric reflux and producing free radicals; while at the same time decreasing prostaglandin and mucus production. Additionally, smoking may reduce lower esophageal sphincter pressure and thus accentuate gastroesophageal-like dyspeptic symptoms.

Risk Factor	Worldwide Prevalence Rate*	United States Prevalence Rate†
Current smoking	10%-31%	19.0%
Overweight (BMI>25 kg/m ²)	34%	34.6%
Obesity (BMI>30 kg/m ²)	9.8% (men)/13.8% (women)	34.6%
Insufficient physical activity (<150 minutes of moderate physical activity/week)	31.3%	21.0%
Poor diet patterns (<4 of 5 DASH-diet components)	N/A	79.0%
High cholesterol (Total cholesterol >240 mg/dL)	9.7%	13.8%
High blood pressure (≥140 SBP/≥90 DBP)	40%	33%
Diabetes (Fasting glucose ≥126 mg/dL)	10%	11.8%

*Rates per the World Heart Federation/World Health Organization [1]

†Rates per the American Heart Association [2]

BMI=body mass index; DASH=Dietary Approaches to Stop Hypertension; DBP=diastolic blood pressure; N/A=not available; SBP=systolic blood pressure

Table 4. Worldwide and United States-Specific Prevalence of Risk Factors for Cardiovascular Disease

While not consistently shown in every study [20-22], smoking's correlation with an increased upper gastrointestinal symptom prevalence (compared to abstainers) has been demonstrated to exist in a fair number of observational studies [8,20,23-25].

In an Australian study of 592 survey respondents of which 78 were dyspeptic, smoking was found to significantly increase this risk of reporting dyspeptic symptoms by more than 100% [19]. The Domestic/International Gastroenterology Surveillance Study also demonstrated smoking to be associated with a significantly greater prevalence of upper gastrointestinal symptoms (16% increase in relative risk) compared to those whom abstained from smoking; with the results of multivariate analysis suggesting smoking's largest negative effect was on heartburn and regurgitation (gastroesophageal-like) symptom prevalence [8].

Similar results were observed in two studies of United States veterans. In the first study, tobacco use was found to be associated with more symptoms of dyspepsia (odds ratio=1.31, 95% confidence interval, 1.03-1.66)[29]. In the second study, a 62% relative in-

Study, Year (N=)	Study Description	Key Finding
Nandurkar 1998 (N=592)	Healthy blood donors in Sydney, Australia completing the Bowel Symptoms Questionnaire; prevalence rate of upper gastrointestinal symptoms=13.2%	Smoking was an independent risk factor for dyspeptic symptoms (OR=2.1, 95%CI=1.3-3.6)
Stranghelli 1999 (N=5,581)	Respondents of the Domestic/International Gastroenterology Surveillance Study which surveyed urban, adult populations from 10 countries representing seven geographic areas (Canada, the USA, Switzerland, The Netherlands, Italy, Japan and the Nordic countries) using a study-specific symptom checklist; prevalence rate of upper gastrointestinal symptoms=28%	Prevalence rate of upper gastrointestinal symptoms were 30.8% for smokers and 26.5% for non-smokers, p=0.0003; Upon multivariate regression analysis, p<0.05 only for the relationship between smoking and gastroesophageal-like symptoms (p=0.03) and not ulcer- or dysmotility-like symptoms
Dominitz 1999 (N=1,582)	Respondents completing surveys (modified Bowel Disease Questionnaire) at one of 4 Durham, NC, USA Veterans Administration clinics; prevalence rate of upper gastrointestinal symptoms=30% (general medicine) to 53% (gastroenterology) depending on site of recruitment	Tobacco use was significantly associated with dyspeptic symptoms (OR=1.31, 95%CI=1.03-1.66)
Locke 1999 (N=1,524)	Cross-sectional survey study of Olmstead County, Minnesota residents completing the gastroesophageal reflux questionnaire; prevalence rate of frequent upper gastrointestinal symptoms=20%	Multivariate adjusted RR=1.3, 95%CI=0.8-2.1 for current vs. never smokers and OR=1.6, 95% confidence interval, 1.1-2.3 for past vs. never smoker
Shaib 2004 (N=465)	Employees of the Houston Veterans Affairs Medical Center, Texas, USA, completing the Gastro Esophageal Reflux Questionnaire; prevalence rate of upper gastrointestinal symptoms=31.4%	41.4% of dyspeptics (including those with gastroesophageal-like symptoms) were smokers vs. 25.6% non-dyspeptics; when gastroesophageal-like symptoms were excluded, no significant relationship between dyspeptic symptoms and smoking was seen (p=0.2)

CI=confidence interval; OR=odds ratio; RR=relative risk

Table 5. Summary of Studies Suggesting an Association Between Smoking and Upper Gastrointestinal Symptoms

crease in dyspepsia symptom reporting in smokers (41.4%) compared to non-smokers (25.6%) was observed. Again, as in the Domestic/International Gastroenterology Surveillance Study [8], subanalysis of the latter study suggested tobacco smoking may have a more profound effect on heartburn and regurgitation symptoms, as evidenced by the fact

that the relationship between smoking and upper gastrointestinal symptom prevalence was no longer statistically significant when patients suffering gastroesophageal-like symptoms (~50% of the study population) were excluded from the analysis ($p=0.2$). This finding is further supported by a survey study conducted in Olmstead County, Minnesota where residents demonstrating current or past smoking increased respondents' risk of gastroesophageal symptoms by 30-60% [25].

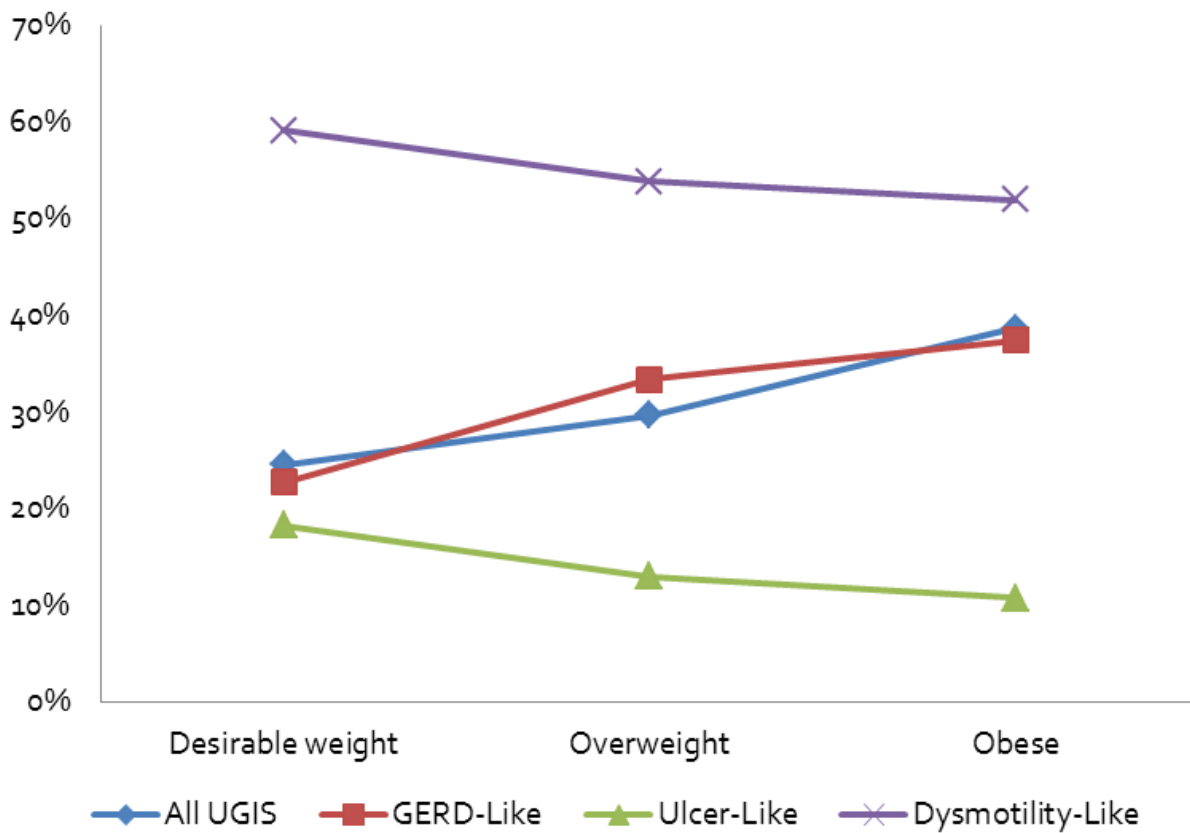
3.2. Overweight or obesity

Overweight (body mass index ≥ 25 kg/m²) or obesity (body mass index ≥ 30 kg/m²) are highly prevalent disorders worldwide and are particular problems in the United States [1,3]. Obesity is strongly related to major cardiovascular risk factors such as elevated blood pressure, glucose intolerance, type 2 diabetes and dyslipidemia. Prospective studies have shown a significant relationship between overweight or obesity and an increased rate of cardiovascular events. In a collaborative meta-analysis of 58 cohorts (221,934 people from 17 countries, 14,297 incident cardiovascular disease outcomes, 1.87 million person-years at risk), patients' risk of coronary heart disease, ischemic stroke and cardiovascular disease were found to increase by 29%, 20% and 23%, respectively, for every 4.56 kg/m² increase in body mass index after adjustment for age, gender, and smoking status [26].

The mechanism behind the association between overweight/obesity and increased upper gastrointestinal symptoms is likely multifactorial [22]. First, the poor diet (ie, increased intake of fatty foods) [22] and lack of exercise that leads the overweight/obese state also promotes increased upper gastrointestinal symptoms (see further discussion below). Next, it is possible that abdominal obesity may lead to gastric compression by the surrounding adipose tissue. This causes increased intragastric pressure and relaxation of the lower esophageal sphincter, and ultimately heartburn and regurgitation. Obesity may also lead to the development of hiatal hernia promoting regurgitation symptoms. Lastly, humoral mechanisms related to obesity including increased levels of insulin, leptin, growth factors or hormones may contribute to gastrointestinal symptoms as well [22,27].

Results of the Domestic/International Gastroenterology Surveillance Study [3] suggested that the prevalence of upper gastrointestinal symptom reporting was higher in those with larger body mass indices. However, consistent with the proposed mechanisms listed above, it appeared the majority of the increased symptom burden related to increased body mass was gastroesophageal-like in nature.

In a meta-analysis of 9 studies examining the association between body mass index and gastroesophageal-like symptoms, six (67%) found a statistically significant association. Furthermore, data from 8 of the 9 studies demonstrated a "dose-response relationship" between body mass index and gastroesophageal symptoms, with an increase in the pooled adjusted odds ratios for symptoms of 1.43 (95% confidence interval, 1.158 to 1.774) for body mass index of 25 kg/m² to 30 kg/m² and 1.94 (95% confidence interval, 1.468 to 2.566) for body mass index ≥ 30 kg/m² [28].



UGIS=upper gastrointestinal symptoms

Figure 2. Prevalence of Upper Gastrointestinal Symptoms (By Subtype) By Body Mass Index in the Domestic/International Gastroenterology Surveillance Study [3] Gastroesophageal-like symptoms are the only symptom subtype trending upwards with increasing body mass index

3.3. Insufficient physical activity

Current guidance [1,29] recommends all adults should do at least 150 minutes a week of moderate-intensity aerobic physical activity, 75 minutes a week of vigorous-intensity aerobic physical activity, or some equivalent combination of both in order to reduce their risk of heart disease and diabetes. In fact, maintaining this level of moderate- or vigorous-intensity physical activity each week has been associated with as much as a 30% decrease in ischemic heart disease risk and a similar reduction (27%) in the risk of developing diabetes. Unfortunately, nearly a third of people worldwide and a fifth of Americans do not meet this goal [1,3]. While the mechanism behind how insufficient physical activity/sedentary lifestyle is associated with upper gastrointestinal symptoms is unclear, it may be that there is a higher rate of overweight/obesity in those who do not engage in enough physical activity, or the failure of inactive people to obtain the mental (reduced stress, reduced depressive symptoms and increased cognitive function) and bodily health benefits borne from physical activity [29].

Limited data evaluating the impact of physical activity on the prevalence of upper gastrointestinal symptoms have been published in the medical literature. In an internet survey of over

2,500 respondents complaining of functional dyspepsia (or other gastrointestinal symptoms), only 6% of respondents reported exercising daily, 29% reported exercising at least once a week, and a majority (54%) claimed almost never or never exercising [30]. This was significantly less physical activity compared to a simultaneously surveyed control population (n=1,000) ($p<0.01$), suggesting that a sedentary lifestyle may be associated with an increased prevalence of upper gastrointestinal symptoms.

3.4. Poor diet patterns

Improper or poor diet has been shown to be an important risk factor for cardiovascular disease. From a strict cardiovascular viewpoint an ideal diet consists the consumption of ≥ 4.5 cups per day of fruits and vegetables, ≥ 2 servings a week of fish, and ≥ 3 servings per day of whole grains and no more than 36 ounces per week of sugar-sweetened beverages and 1500 mg per day of sodium [31]. In addition, other poor diet choices such as high dietary intake of saturated fat, trans-fat and cholesterol have also been tied to poor cardiovascular outcomes [1].

The failure to meet the above-mentioned dietary and lifestyle goals not only hinders a person's ability to achieve a healthy body weight, desirable cholesterol profile, and blood pressure, but has also been linked to increased rates of upper gastrointestinal complaints. In a retrospective database analysis [9] of employed Americans with functional dyspepsia determined by having an ICD-9 code of 536.8x (n=1,669) and matched controls (n=83,450), those found to have a nutritional deficiency (defined by the Agency of Healthcare Research and Quality's Clinical Classifications Software grouping of relevant ICD-9 codes) were 3.8-times as likely to complain of dyspeptic symptoms ($p<0.05$). Moreover, in the previously mentioned survey study of >2,500 respondents complaining of dyspeptic or irritable bowel symptoms and 1,000 controls [30], the irregular eating of meals was found to be associated with increased gastrointestinal complaints ($p<0.05$).

A handful of observational studies have also more specifically evaluated the individual contributions of various components of poor diet on upper gastrointestinal symptom prevalence. An insufficient intake of vegetables has been found to be statistically significantly associated with increased gastrointestinal complaints ($p<0.05$) [30]. Moreover, in a sample of 1,000 employees of the United States Veteran's Administration system, a strong trend ($p=0.09$) towards an increased prevalence of heartburn and regurgitation symptoms (adjusted odds ratio=1.71, 95% confidence interval, 0.92-3.17) in those with high intake of saturated fat (measured using the 100-item Block Food Frequency Questionnaire) was also observed [22].

3.5. High cholesterol and high blood pressure

Ten percent of the world's adult population (and nearly 14% of the United States population) have high cholesterol (total cholesterol ≥ 240 mg/dL) and more than one-third of all people have high blood pressure (systolic and diastolic blood pressure ≥ 140 and 90 mm Hg, respectively), including 77.9 million American adults. Approximately one third of the global burden of ischemic heart disease can be attributed to high cholesterol, and each 20/10 mmHg increase in blood pressure, starting at 115/75 mmHg, has been shown to double a patients' risk of a

cardiovascular event. The treatment of both high cholesterol and high blood pressure often necessitates polypharmacy [32,33], and many of the drugs used to treat these conditions may cause upper gastrointestinal symptoms (see further discussion below).

There are conflicting data regarding the association between high cholesterol, high blood pressure and upper gastrointestinal symptoms. In one recent retrospective database analysis of 4-years' worth of data on 300,000 employees of companies in the United States-based, patients with ICD-9 codes for functional dyspepsia symptoms (n=1,669) were found to have a higher rate of both high cholesterol (prevalence rates of 21.2% versus 12.1%, $p<0.05$) and essential hypertension (17.8% versus 12.4%, $p<0.05$) compared to matched controls without upper gastrointestinal symptom coding (n=83,450) [9]. However, in a far older study examining nearly 5,000 adults in the Rand Health Experiment, no statistically significant association was observed between either hypercholesterolemia or hypertension and patient reporting of "episodes or attacks of stomach pain or stomachache" in the prior 3-months [11].

3.6. Diabetes

In 2008, the global prevalence of diabetes (fasting plasma glucose ≥ 126 mg/dL) was estimated to be 10%, resulting in approximately 1.3 million deaths. A diagnosis of diabetes increases patients' risk of cardiovascular disease by 2- to 3-fold, and consequently, cardiovascular disease accounts for approximately 60% of all diabetes-related deaths [1].

Diabetes may increase peoples' risk of having upper gastrointestinal complaints for a number of reasons. First, many medications used to treat diabetes and hopefully reduce patient's risk of both cardiovascular and microvascular (retinopathy, neuropathy, nephropathy) complications can cause upper gastrointestinal symptoms including biguanides, sulfonylureas and alpha-glucosidase inhibitors [34]. Next, abnormal glucose regulation tends to occur in conjunction with other cardiovascular risk factors such as obesity, elevated blood pressure, low high-density lipoprotein cholesterol and a high triglyceride levels [1], as well as psychiatric disorders [35]; all known to be risk factors for upper gastrointestinal symptoms. Finally, the neuropathy associated with diabetes and resulting gastroparesis may cause diabetics to suffer from more upper gastrointestinal problems [35]. A recent prospective cohort study of 782 individuals found that *Helicobacter pylori* infection (a common cause of upper gastrointestinal symptoms) was associated with a 2.69-fold increased hazard of developing type II diabetes (95% confidence interval=1.10-6.60) [36], suggesting the relationship between diabetes and upper gastrointestinal symptoms may be bidirectional.

Some studies support the association between diabetes and upper gastrointestinal symptoms. The Domestic/International Gastroenterology Surveillance Study demonstrated those suffering from a metabolic or endocrine disorder (which would presumably include in large part, diabetes) were 2.6- to 4.4-fold more likely to report upper gastrointestinal symptoms in the prior three months ($p<0.006$) [8]. A study of Swedish type II diabetics (n=61) and non-diabetics (n=106) asked to complete a gastrointestinal symptom checklist found type II diabetics were more likely to report abdominal pain more often than once a month (28.3% versus 14.3%, $p<0.01$) and heartburn (31.77% versus 14.0%, $p<0.05$) [37]. Interestingly, it appears that the prevalence of upper gastrointestinal symptoms in diabetics may be linked to the extent/

severity of their disease, with a large (n=1,101) cross-sectional survey study demonstrating higher adjusted odds of frequent abdominal pain (odds ratio=1.62, 95% confidence interval, 1.02-2.58), dysmotility-like dyspepsia (odds ratio=2.01, 95% confidence interval, 1.30-3.11), ulcer-like dyspepsia (odds ratio=1.49, 95% confidence interval, 0.90-2.45) and gastroesophageal reflux symptoms (odds ratio=2.28, 95% confidence interval, 1.54-3.38) in patients experiencing a diabetes-related complication compared to those whom did not, and higher adjusted odds of dysmotility-like dyspepsia (odds ratio=1.32, 95% confidence interval, 1.08-1.60), ulcer-like dyspepsia (odds ratio=1.36, 95% confidence interval, 1.06-1.75) in those with poorer hemoglobin A1c control [38].

Appropriate management of the overlapping risk factors can result in additional benefit to the patients. Of the many care management decisions to be made between the health care providers and the patients, an understanding of the risk factor pattern can help with the prioritization. These overlapping risk factors may deserve a higher priority, as they will improve both the cardiovascular and upper gastrointestinal conditions at the same time.

4. Overlapping symptomatology and surveillance

As many as 40% of people will complain of chest pain (along with associated symptoms of nausea, palpitations and shortness of breath) at least once in their lifetime [39,48]; however, symptoms reported by patients are typically unreliable for differentiating between chest pain of a cardiac or gastrointestinal (ie, dyspepsia, gastroesophageal reflux, peptic ulcer disease, pancreatitis, cholecystitis) origin [39,49]. Hence, the birth of famous adages such as, “*when a young man complains of pain in his heart, it is usually his stomach; when an old man complains of pain in his stomach, it is usually his heart*” [39]. Upper gastrointestinal symptoms, particularly gastroesophageal- or dysmotility-like dyspeptic symptoms, are a frequent cause of non-cardiac chest pain (ie, recurrent episodes of substernal chest pain in patients lacking a cardiac diagnosis after a comprehensive evaluation) [39]. This likely explains why as many as 55% of chest pain sufferers presenting to the emergency room for the first time are not ultimately diagnosed with cardiovascular disease [50], and 30% of patients undergoing coronary angiography each year show no signs of coronary heart disease [51]. However, despite the lack of a cardiac diagnosis, up to 80% of non-cardiac chest pain sufferers continue to experience symptoms over time, and 25%-45% continue to take antianginal medications [52]. Thus, because of the critical and continual need to differentiate between cardiovascular disease and upper gastrointestinal symptoms in patients with chest pain, it would seem reasonable to assume the increased surveillance of one of these disorders would result in a higher rate of diagnosis of the other.

It has been suggested that in areas with a high prevalence of *H. pylori* infection, a “search and treat” strategy for ischemic heart disease patients with dyspepsia could significantly reduce the need for urgent postoperative endoscopy due to major gastrointestinal events [53]. However, endoscopy has been shown to induce cardiovascular complications, including myocardial ischemia [40,41,54]. Thus, this practice may serve as an additional explanation for the frequent diagnosis of cardiovascular disease in patients experiencing upper gastrointesti-

nal symptoms. An early study [54] of 110,469 upper endoscopies performed by 82 gastroenterologists and 12 internists found a rate of 5 cardiopulmonary complications (not specifically defined) per 100,000 procedures performed. However, more recent studies in patients with stable coronary disease or those at risk for cardiovascular disease have observed much higher rates of cardiovascular complications following endoscopy. In a study of 71 patients with stable coronary heart disease undergoing endoscopy for evaluation for the safety of secondary prophylaxis with aspirin, 42% of patients experienced silent ischemia and one patient had a symptomatic event [40]. A second study utilizing data from 9 hospitals in the United States evaluated 602 charts for patients undergoing endoscopy and deemed to be at risk for cardiovascular disease. The researchers found an overall cardiovascular complication (either an arrhythmia, hypotension, chest pain or angina equivalent, or myocardial infarction requiring intervention and occurring within one calendar day after the endoscopy) rate of one for every 325 procedures (or 308 complications per 100,000), and a rate as high as one complication for every 94 procedures (1,063 complications per 100,000) at the worst performing hospital [41]; a complication rate 2- to 70-fold higher than previously reported in the medical literature.

The awareness of how the symptoms of cardiovascular diseases and upper gastrointestinal conditions overlap can improve the differential diagnosis, thus reducing the chance of inappropriate procedures and medications.

5. Adverse effect of cardiovascular drugs

Optimal treatment of patients with cardiovascular disease [32,33] often requires the use of multiple medications. Consequently, at least some of the burden of upper gastrointestinal symptoms experienced in patients suffering from cardiovascular disease may be a result of polypharmacy. In the aforementioned Domestic/International Gastroenterology Surveillance Study [8], the occurrence of upper gastrointestinal symptoms was significantly higher in respondents reporting the use of a prescribed medication for another health problem compared to those not prescribed a medication (10.6% versus 6.0%, 5.1% versus 3.5% and 19.1% versus 13.3% for gastroesophageal-, ulcer- and dysmotility-like symptoms, respectively, multivariate $p < 0.007$ for all). Likewise, the use of an over-the-counter medication was also associated with a higher rate of upper gastrointestinal symptoms in general and dysmotility-like symptoms (19.3% versus 13.2% and 33.9% versus 24.6%; $p < 0.0001$ for both).

Numerous drugs indicated or commonly used to treat cardiovascular diseases including antiplatelets, antiarrhythmics, antihypertensives, antianginals, cholesterol-lowering medications, as well as drugs to manage heart failure, diabetes and chronic kidney disease have been linked to the development of upper gastrointestinal symptoms.

Unfortunately, drug-induced dyspepsia can be difficult to identify because of the high background reporting of upper gastrointestinal symptoms. To overcome this problem, two studies [42,43,45] were conducted in a Dutch prescription database of over 1.5 million prescriptions (92 million person-years of follow-up) to identify signals for drug-induced dyspepsia using prescription sequence symmetry analysis methods. The basic principle

behind these types of analyses is that most patients complaining of drug-induced dyspeptic symptoms are empirically treated with anti-ulcer and/or anti-dysmotility agents; therefore, a drug's propensity for causing upper gastrointestinal symptoms might be reflected in the sequencing of anti-ulcer and/or anti-dysmotility agents relative to the other medication (eg, an excess of patients presenting with their first prescription for an anti-ulcer or dysmotility agent after compared to before the initiation of an index drug would suggest a possible dyspepsia-causing effect of the index drug). These studies identified a handful of (index) drugs to treat cardiovascular disease that were more often followed by (within 100-days), as compared to preceded by a histamine-2-antagonist, proton pump inhibitor, bismuth preparation, sucralfate, cispiride or metoclopramide. Drugs used to treat heart failure were among the drugs with the largest relative risks for upper gastrointestinal symptoms.

Cardiovascular Drug(s)	Common Cardiovascular Indication(s)
Acetylsalicylic acid (and other NSAIDs)	Antiplatelet
Amiodarone	Antiarrhythmic
Amlodipine (and other calcium channel blockers)	Antihypertensive, antianginal
Atorvastatin (and other statins)	High cholesterol
Beta-blockers	Antihypertensive, antianginal, heart failure
Bile acid sequestrants (less often with colestevam)	High cholesterol
Non-aspirin antiplatelet agents (ie, cilostazol, ticlopidine)	Antiplatelet
Fibric acid derivatives (gemfibrozil>fenofibrate)	High cholesterol
Fish oil preparations (ie, omega-3 fatty acids)	High cholesterol, dietary supplement
Digoxin	Atrial fibrillation, heart failure
Dronedarone	Antiarrhythmic (atrial fibrillation)
Loop diuretics	Heart failure, chronic kidney disease
Losartan	Antihypertensive, heart failure, diabetes, chronic kidney disease
Niacin and nicotinic acid derivatives	High cholesterol
Nitrates	Antianginal
Potassium supplements	Dietary supplement
Ramipril (and other ACE inhibitors)	Antihypertensive, heart failure, diabetes, chronic kidney disease

This list was derived from searches of references 41,42,44,54,55

ACE=angiotensin-converting enzyme; NSAID=non-steroidal anti-inflammatory

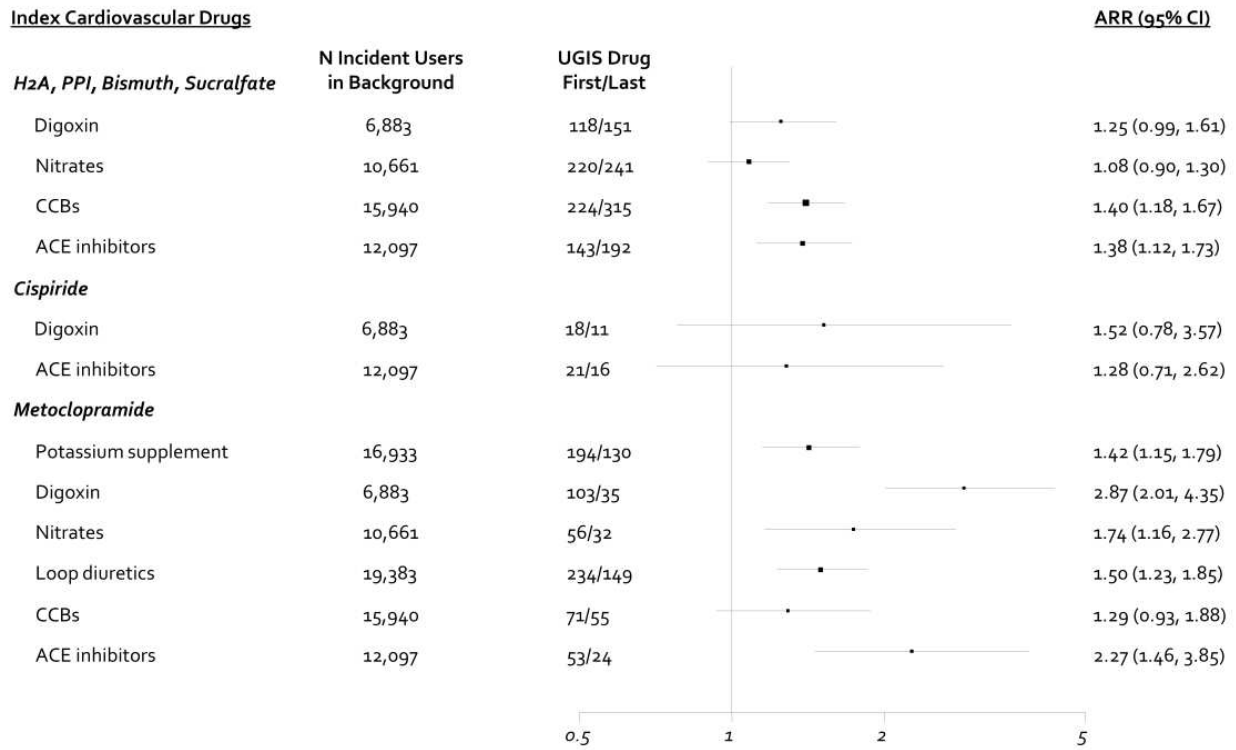
Table 6. Cardiovascular Drugs Commonly Associated With Upper Gastrointestinal Symptoms

While a plausible explanation or underlying mechanism by which the abovementioned cardiovascular drugs can cause upper gastrointestinal symptoms is not always apparent, these drugs likely induce symptoms through direct mucosal irritation or injury (ie, aspirin and other non-steroidal anti-inflammatory drugs, potassium supplementation), facilitation of gastric acid reflux (ie, calcium channel blockers, nitrates) or alteration of gastric motility (ie, drugs targeting the renin-angiotensin system causing bradykinin-mediated dysmotility) [45,55]. Still yet, other associations between cardiovascular drugs and upper gastrointestinal symptoms may be “false” signals, representing nothing more than a link between a specific disease state or other confounder and upper gastrointestinal symptoms. Such may be the case with cholesterol-lowering medications. Patients with hypercholesterolemia may prefer frequent consumption of high-fat meals a well-known independent predictors of higher gastroesophageal symptom prevalence rates. [22,42,43,45].

Similarly, while drugs commonly used to treat heart failure, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics and digoxin, have also been demonstrated in prescription sequence symmetry analyses to be upper gastrointestinal symptom-inducing; it is likely the symptoms attributed to them are a manifestation of heart failure itself (which has previously been shown to increase the risk of ulcer-like symptoms by as much as 3.6-fold [11]) and not the individual medications [11,57]. Of note, this may not always be the case with digoxin, which has been associated with dyspeptic-like symptoms in patients experiencing elevated/toxic blood concentrations (>2.0 ng/mL) [58].

Each year about 400,000 tons of aspirin (acetylsalicylic acid) are produced worldwide, and >50 million Americans take between 10 and 20 billion tablets for cardiovascular disease prevention [59]. Aspirin becomes non-ionized in the acidic environment of the gastrointestinal tract allowing it to penetrate mucosal tissue and cause irritation. Consequently it is not surprising that numerous studies have demonstrated aspirin to increase patients’ relative risk of upper gastrointestinal symptoms by more than 2-fold over non-users [19-21,24,44]. Because of aspirin’s frequent use and its propensity to cause gastric mucosal injury, it is likely the biggest drug-induced dyspepsia offender and one of the strongest links between upper gastrointestinal symptoms and cardiovascular disease. While it is best to stop aspirin in light of gastrointestinal symptoms, there may be adverse cardiovascular consequences that need to be considered. A double-blind, placebo-controlled study evaluating low-dose aspirin users who experienced gastrointestinal bleeding compared continuation of aspirin with discontinuation [60]. Seventy-eight patients received aspirin 80 mg daily while 78 received placebo daily for 8 weeks. All patients received intravenous followed by oral proton pump inhibitor therapy (intravenous pantoprazole 80 mg bolus followed by 8 mg/hour for 72 hours then oral pantoprazole 40mg daily). Recurrent bleeding occurred in 10.3% of patients in the aspirin group vs. 5.4% of those in the placebo group (difference=4.9 points, 95% confidence interval=-3.6 to 13.4), *p*=not significant), but patients who received aspirin had lower all-cause mortality rates than patients who received placebo (1.3% vs. 12.9%, difference=11.6 points, 95% confidence

interval=3.7 to 19.5). As such, if aspirin must be part of the regimen, like in settings where dual antiplatelet therapy is needed (cardiac stenting, post unstable angina and myocardial infarction), treating the adverse gastrointestinal effects may be a superior strategy.



ACE=angiotensin-converting enzyme; ARR=adjusted rate ratios; CCBs=calcium channel blockers; CI=confidence intervals; H2A=histamine-2-antagonist; PPI=proton pump inhibitor; UGIS=upper gastrointestinal symptoms

Figure 3. Results of Cardiovascular Drug Sequence Symmetry Analyses Using Histamine-2-Antagonists, Proton Pump Inhibitors, Bismuth Preparations or Sucralfate, Cispiride or Metoclopramide. The cardiovascular sequence symmetry analyses depicted above assumed the development of one or more upper gastrointestinal symptoms was followed by (within 100 days) the prescription of a drug to treat it (eg, a histamine-2-antagonist, proton pump inhibitors, bismuth preparation or sucralfate, cispiride or metoclopramide). Results were reported as the adjusted rate ratio of individuals with an upper gastrointestinal symptom-treating drug prescribed last versus individuals with the upper gastrointestinal symptom-treating drug prescribed first. Ratios above 1.0 indicate a possible upper gastrointestinal symptom-inducing effect of the index cardiovascular drug.

Of note, while studies suggest enteric-coated or buffered formulations of aspirin provide no significant protective effect against gastrointestinal complications [61], randomized trials of patients taking aspirin suggest concomitant proton pump inhibitor therapy can both prevent upper gastrointestinal symptoms ($p < 0.05$) [62] and reduce their prevalence in patients already suffering dyspeptic symptoms [44,62].

Aspirin is not, however, the only antithrombotic agent that has been associated with upper gastrointestinal symptoms. In fact, both non-aspirin antiplatelet agents (including other non-steroidals, P2Y12 platelet inhibitors and phosphodiesterase inhibitors) and anticoagulants (particularly oral direct thrombin inhibitors) have been associated with clinically important

UGIS	PPI Group	Placebo Group
Epigastric pain	83.9%	66.7%*
Epigastric burning	72.7%	58.1%
Epigastric discomfort	68.3%	50.9%*
Heartburn	89.7%	66.7%*
Acid reflux	86.4%	56.5%*
Nausea	92.6%	78.6%
Bloating	77.9%	66.1%

*p≤0.05

PPI=proton pump inhibitor; UGIS=upper gastrointestinal symptoms

Table 7. Percentages of Patients Taking Aspirin (75-325 mg/day) and Suffering Upper Gastrointestinal Symptoms Reporting Resolution of Symptoms Following 26-Weeks of Proton Pump Inhibitor (Esomeprazole 20 mg/day) Therapy or Placebo [62]

rates of upper gastrointestinal symptoms [46,47,63]. In the largest systematic review to date (92 controlled trials), non-steroidals were found to increase the risk of dyspepsia versus placebo regardless of whether a strict (relative risk=1.36, 95% confidence interval=1.11-1.67) or liberal definition (relative risk= 1.19, 95% confidence interval=1.03-1.39) was used; with a placebo rate of 2.3% using the strict definition and 4.2% using the liberal definition [63].

In a systematic review of randomized controlled trials of adults with atrial fibrillation receiving pharmacologic stroke prevention, not only were upper gastrointestinal adverse effects found to be common place, but oral direct thrombin inhibitors were associated with highest incidences of (~11%) and drug discontinuation due to these symptoms (~2%) [46]. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study found a statistically higher incidence of dyspepsia in patients receiving the oral direct thrombin inhibitor, dabigatran, compared to adjusted-dose warfarin (11.8% for dabigatran 110 mg, 11.3% for dabigatran 150 mg and 5.8% for warfarin, p<0.001 for the comparison of either dose of dabigatran versus warfarin)[47]. The dyspepsia-provoking nature of dabigatran has been attributed to its formulation which utilizes a tartaric acid core to lower the pH in the gastrointestinal tract and thus increase the absorption of the drug [47]. Luckily, there are Factor Xa inhibitors as therapeutic alternatives to direct thrombin inhibitors in those impacted by, or likely to be impacted by, upper gastrointestinal symptoms [56,64].

Beyond the ability of cardiovascular drugs to provoke upper gastrointestinal symptoms, the occurrence of these symptoms may adversely affect cardiovascular drug adherence, putting

Agent	Mechanism of Action	UGIS	Nausea
<i>Antiplatelet agents</i>			
ASA	Blockade of COX-1	++++ (>6%)	++++ (>6%)
Non-ASA NSAIDs	Blockade of COX-1	+++ (ibuprofen, naproxen: 2-3%); ++++ (indomethacin: >6%)	+++/++++ (drug dependent: 3-9%)
Cilostazol	PDE III blockade	++++ (~6%)	++++ (~7%)
Clopidogrel	P2Y12 inhibition	++ (<2%)	++ (<2%)
Prasugrel	P2Y12 inhibition	++ (<2%)	+++ (~5%)
Ticagrelor	P2Y12 inhibition	++ (~2%)	+++ (~4%)
Ticlopidine	P2Y12 inhibition	++++ (~7%)	++++ (~7%)
<i>Anticoagulant agents</i>			
Warfarin	Vitamin K antagonist	++++ (6%)	++ (1.5%)
Dabigatran	Direct thrombin inhibition	++++ (11%)	NA
Rivaroxaban	Factor Xa inhibition	++ (≤2%)	++ (2%)
Apixaban	Factor Xa inhibition	NA	+++ (3%)

++=minimal risk (≤2%); +++=moderate risk (3-5%); ++++=high risk (5-10%)

ASA=aspirin; COX=cyclooxygenase; NSAID=non-steroidal anti-inflammatory drug; NA=not available; PDE=phosphodiesterase; UGIS=upper gastrointestinal symptoms

Table 8. Cross-Comparison of Upper Gastrointestinal Symptoms Precipitated by Antithrombotics [46,47,56,65]

patients at risk for adverse cardiovascular outcomes. Studies have demonstrated that gastrointestinal side effects decrease medication adherence [66], and this likely plays an important role in the poor adherence often seen across the spectrum cardiovascular medications [67].

6. Cardiovascular disease associated with upper gastrointestinal symptom drug use

In addition to cardiovascular drugs provoking upper gastrointestinal symptoms, a number of medications used to treat upper gastrointestinal symptoms have impacted cardiovascular drug function or have been associated with poor cardiovascular outcomes through both indirect and direct mechanisms.

6.1. Drug interactions impeding cardiovascular drug function

Proton pump inhibitors are frequently used to treat various gastrointestinal symptoms/conditions including *H. pylori* infection. American College of Gastroenterology guidelines recommended strategies for the eradication of *H. pylori* infection include treatment with at

least three drugs, and yield eradication rates of up to 90%. While the best *H. pylori* treatment regimen may vary depending on patient characteristics, guidelines recommended four different drug regimens including a proton pump inhibitor, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days, a proton pump inhibitor or histamine-2-antagonist, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10–14 days, or sequential therapy consisting of a proton pump inhibitor and amoxicillin for 5 days followed by a proton pump inhibitor, clarithromycin, and tinidazole for an additional 5 days (as an alternative to clarithromycin-based triple or bismuth quadruple therapy) [68].

Proton pump inhibitors competitively inhibit the cytochrome P450 2C19 isoenzyme (CYP2C19). Based on in vitro and in vivo data, omeprazole and esomeprazole are the most potent CYP2C19 inhibitors [69]. In vivo, omeprazole and esomeprazole induced 4 and 10 fold functional inhibition of CYP2C19 versus less than 1.5 fold inhibition with lansoprazole and pantoprazole [70]. Rabeprazole has in vitro data showing less inhibition of CYP2C19 than omeprazole and lansoprazole but no in vivo data is available [69].

Clopidogrel is a CYP2C19 substrate and needs to be activated by this isoenzyme. When given concurrently with proton pump inhibitors, there is a reduction in the produced active form of clopidogrel and greater platelet reactivity (less platelet inhibition) [71,72].

Whether this platelet reactivity effect impacts clinical events has been controversial. A 2009 population-based study among Ontario residents aged 66 years or older used prescription records to ascertain proton pump inhibitor use during clopidogrel therapy. The analysis suggested that proton pump inhibitor use may be associated with an increased risk of cardiovascular events [odds ratio for recurrent myocardial infarction within 90 days following hospital discharge, 1.27 (1.03 to 1.57)], however, no effect on the risk of death was observed [odds ratio of death within 90 days following hospital discharge 0.82 (0.57 to 1.18)] [73]. The 16,718 patient Clopidogrel Medco Outcomes Study was a cohort evaluation from an integrated medical and pharmacy claims database. Patients had a clopidogrel prescription filled within one month of a coronary stenting procedure (where dual aspirin and clopidogrel therapy is frequently employed). Patients who concomitantly received a proton pump inhibitor were in the active group while those without were in the control group in this observational non-randomized study. Those receiving a proton pump inhibitor had more cardiovascular events (myocardial infarction, unstable angina, repeat coronary procedure) than those without (25% vs. 18%, $p < 0.0001$). Without randomization, however, it cannot be ascertained where it was the underlying patient population with gastrointestinal symptoms that had a higher risk or if the use of the proton pump inhibitor yielded the difference. When patients on each proton pump inhibitor were analyzed separately, there were no differences in the percent of patients with a cardiac event: omeprazole 25%, esomeprazole 25%, lansoprazole 24%, and pantoprazole 29%. Given the marked differences in CYP2C19 inhibition between omeprazole and esomeprazole versus lansoprazole and pantoprazole, qualitative differences between the groups would have been expected [74]. Two other smaller analyses also supported the greater risk of cardiac events with patients receiving concurrent proton pump inhibitors but again, whether

the additional risk is due to the underlying differences in the populations versus the use of the drug cannot be determined [75,76].

In the 13,608 patient TRITON-TIMI 38 Trial, a third of patients were on a concomitant proton pump inhibitor (41% pantoprazole, 37% omeprazole, 14% esomeprazole, 10% lansoprazole, 1% rabeprazole). In a nested cohort analysis from this trial, there was no difference between the proton pump inhibitor group and the control group for the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke [77].

Given the profound effect of confounders, especially co-linear confounders, on the results of observational trials, these trials cannot prove causality, regardless of their results. Randomized and placebo controlled clinical trials eliminate many of these confounders and have much stronger internal validity. The only major randomized evaluation of the impact of proton pump inhibitors on cardiovascular events was the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial. Overall, 3761 patients starting dual antiplatelet therapy with aspirin and clopidogrel were randomized to receive omeprazole or placebo. No difference was found in the primary composite cardiovascular endpoint ($p=0.98$) but the rate of overt upper gastrointestinal bleeding was reduced with omeprazole therapy versus placebo [hazard ratio 0.13 (0.03 to 0.56)] [78]. The use of omeprazole which is the most potent CYP2C19 inhibitor was the best proton pump inhibitor choice to evaluate the balance of benefits to harms in this population [56, 69].

The COGENT trial and TRITON-TIMI 38 analysis results led the American College of Cardiology, American College of Gastroenterology, and American Heart Association to issue guidelines calling for the use of proton pump inhibitors when indicated for patients receiving antiplatelet therapy for cardiovascular disease [79]. However, the package insert recommends avoiding the use moderate to strong CYP2C19 inhibitors and to use alternative acid suppressing agents such as H2 antagonists or less potent CYP2C19 inhibiting proton pump inhibitors where possible [56].

Aside from proton pump inhibitors, the histamine-2 antagonist cimetidine is ubiquitous moderate CYP 1A2, 2C19, 2D6, and 3A4 inhibitor [56]. It raises the concentrations of all these cardiovascular medications increasing the chances for cardiovascular adverse effects. As such additional monitoring is suggested when added to amiodarone, beta-blockers (carvedilol, nebivolol), calcium channel blockers (verapamil, diltiazem, nifedipine), procainamide, propafenone, and ranolazine while selection of an alternative agent is specifically suggested when quinidine is being used. Other drugs in this class do not have the same potency of inhibition and are therapeutic alternatives [56].

6.2. QTc prolongation and Torsade de Pointes

Two classes of commonly used upper gastrointestinal drugs impact QTc prolongation and arrhythmogenesis. The QTc interval is a marker of ventricular depolarization and repolarization time and if the QTc interval reaches 500ms or is elevated by 60ms over baseline values, the risk of the polymorphic ventricular arrhythmia Torsade de Pointes is elevated [80]. Torsade de Pointes can be a life threatening arrhythmia and requires prompt detection and treatment.

Cisapride is a promotility agent that enhances acetylcholine release at the myenteric plexus [56]. In March of 2000, the Food and Drug Administration was notified that the manufacturer would stop widespread manufacture of the drug due to elevated risk of QTc interval prolongation and the formation of the polymorphic ventricular tachycardia Torsade de Pointes. There are 341 reports of heart rhythm abnormalities, likely Torsade de Pointes, and 80 deaths with cisapride. It is still being made and distributed to individuals for whom other options have failed but is contraindicated with QTc interval prolonging agents such as Vaughn Williams Class Ia (quinidine, procainamide) or Class III (amiodarone, dronedarone, sotalol, dofetilide) antiarrhythmic agents, macrolide antibiotics (erythromycin, clarithromycin, troleandomycin), nefazodone, HIV protease inhibitors, and -azole antifungals. It is also contraindicated with potent CYP3A4 inhibitors and prone individuals [56, 80]. While not classically considered a gastrointestinal drug, erythromycin stimulates motilin receptors and can be an adjunctive promotility agent in diabetic gastroparesis. Erythromycin blocks the rapid component of the delayed rectifier potassium channel and prolongs the QTc interval and arrhythmogenic risk as well [80].

The 5HT₃ antagonists (dolasetron, granisetron, etc) prolong the QTc interval and when used intravenously or in patients with other QTc interval prolonging drugs, hypokalemia or hypomagnesemia, or congenital long QT syndrome; can induce the polymorphic ventricular arrhythmia known as Torsade de Pointes [80]. Correcting electrolyte abnormalities before starting a 5HT₃ antagonist is important in preventing Torsade de Pointes but is also sometimes difficult given the emesis the drugs are being used to control [56].

6.3. Bradycardia and atrioventricular blockade

The 5HT₃ antagonists (dolasetron, granisetron, ondansetron, etc) and the histamine 2 receptor antagonists (cimetidine, ranitidine) have been shown to rarely cause negative chronotropic (reduced sinoatrial nodal firing rate) and dromotropic (reduced rate of impulse passage through the atrioventricular node) effects when used in excessive doses or in intravenous forms [56, 80]. Patients who are prone to develop bradycardia or heart block, such as those with borderline low heart rates, elevated baseline PR intervals, or are receiving other negative chronotropic or dromotropic drugs (beta-blockers, nondihydropyridine calcium channel blockers, digoxin, Vaughn Williams Class Ic antiarrhythmic agents) are most at risk [56,80].

6.4. Hypertension

Metoclopramide is a complex dopaminergic agent with differing effects on blood pressure in different individuals. When used as a sole agent in normotensive, essential hypertensive, and type 2 diabetic subjects, there is no effect on systolic or diastolic blood pressure [81,82]. However, it can profoundly elevate blood pressure in patients with pheochromocytoma and in patients developing serotonin syndrome while taking metoclopramide with select serotonin reuptake inhibitors [83-86]. In addition, it has been shown to modestly attenuate the antihypertensive effects of bromocriptine and labetalol [87,88]. In this way, metoclopramide can induce hypertensive urgencies and emergencies in prone individuals and alternative agents should be utilized when appropriate.

The consequences of these drug-disease interactions can be dire, with significant impact on mortality and morbidities. As many of these interactions are unknown until a large population has been using the offending medications, health care providers must remain vigilant in identifying potential new problems.

7. Conclusions

There is growing evidence that patients with cardiovascular disease suffer a higher burden of upper gastrointestinal symptoms and even that certain upper gastrointestinal complaints can induce or promote cardiovascular disease. Knowledge of how these common conditions are connected can bring forth therapeutic advantages. For instance, among patients with upper gastrointestinal symptoms, their interactions with the health care system can increase the chance of earlier diagnosis of cardiovascular conditions. Conversely, among patients with cardiovascular conditions, health care providers' inquiry into gastrointestinal symptoms and side effects of medications may aid in appropriate choice of therapy to enhance effectiveness and patient adherence. Additional research is needed to clarify whether the cardiovascular patients' increased risk of upper gastrointestinal symptoms is a result of shared pathophysiology or risk factors, increased surveillance due to overlapping symptoms, or induced by the frequent need for polypharmacy among sufferers of both these disease states.

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