Journal of Advances in Medical and Pharmaceutical Sciences

18(2): 1-18, 2018; Article no.JAMPS.44526
ISSN: 2394-1111

Prevalence and Risk Factors of Potential Drug Interactions in Hospitalized Cardiovascular Patients Using Three Knowledge Bases

Heba Y. Raslan[1], Ayman K. M. Hassan[2], Mona M. M. El-Mahdy[3] and Tahani H. Elfaham[3*]

[1]Drug Information Center, Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt.
[2]Department of Cardiovascular Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt.
[3]Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMPS/2018/44526
Editor(s):
(1) Dr. Sam Said, Department of Cardiology, Hospital Group Twente, Hengelo, Netherlands.
Reviewers:
(1) Sheikh Shahnawaz, India.
(2) Luca Gallelli, University of Catanzaro, Italy.
Complete Peer review History: http://www.sciencedomain.org/review-history/26621

Original Research Article

Received 16 July 2018
Accepted 03 October 2018
Published 12 October 2018

ABSTRACT

Background: Drug interactions continue to be an important cause of adverse effects, especially with cardiovascular drugs.
Objective: This cross-sectional observational study aimed to recognize the frequency of potential drug-drug interactions (pDDIs) using three electronic knowledge bases (KBs); Lexicomp®, Micromedex®, and the free Drugs.com®, compare the inclusion and gradings of pDDIs in these three KBs and to identify associated risk factors.
Methods: Medication orders of 125 patients in the cardiovascular department and its intensive care unit (ICU) of Assiut University Hospitals, Egypt were screened for pDDIs.
Results: About 88.8% of the patients were prescribed five or more drugs. A sum of 1206 pDDIs was found which comprised of 245 different interacting pairs. Overall, 96.8% of the patients had at least

**Corresponding author: E-mail: telfaham@aun.edu.eg;*

one pDDI. Moderate risk pDDIs represented the most frequent risk level at 72.24%. Statistical analysis of data by multivariate regression has shown that the number of drugs prescribed could significantly predict the number of pDDIs (p<0.001). This was confirmed by bootstrapped Spearman's correlation (r_s(123)=0.808; bias-corrected and accelerated [BCa] 95% confidence interval, 0.719–0.873; p<0.001). Drugs.com® alerted the largest number of pDDIs. Both Drugs.com® and Lexicomp® have shown that most prevalent pDDIs were moderate and that contraindicated were the least, while the major grading was the largest in Micromedex®.

Conclusion: A high prevalence of pDDIs was detected, and polypharmacy was a major risk factor. Physicians need to determine the most relevant approach to check for pDDIs while balancing between excessive alerting and overriding of interacting drug pairs. the Integration of medication review guidelines and computerized alert systems should be considered.

Keywords: Drug interactions; cardiovascular; medication safety; prevalence; risk factors; hospitalized patients.

1. INTRODUCTION

Multiple drug therapy is essential to treat certain ailments or to manage multimorbidities. Thus, treatment regimens can become complex with the possibility of one drug altering the pharmacokinetics and/or pharmacodynamics of another [1]. While the benefit of drug combinations should always outweigh their risk, the hazard of interactions amongst drugs is predicted to rise when more drugs are co-administered [2].

Drug interactions (DIs) are considered an important form of adverse drug reactions (ADRs) which are reportedly responsible for about 16.6% of ADRs and 1.1% of hospital admissions [3]. If significant pDDIs were inappropriately identified, they could result in undiagnosed ADRs. Nineteen percent of ADRs in a recent investigation by Gallelli et al were inadvertently treated as a newly developed health condition [4].

Covering all prescribing information by physicians becomes challenging since a considerable number of new drugs or generic equivalents are approved yearly [5]. Further particulars on both new and old drugs become available through post-marketing surveillance. Good grasp of evidence-based medicine can allow for safer drug use [6].

Although some interactions can be desirable, most significant DIs are unwanted but are foreseeable and could be monitored or prevented. However, the widespread self-medication of over-the-counter (OTC) drugs and herbal products can complicate treatment with prescription medications which renders it necessary to include in medications checks [7].

The incidence of clinically significant DIs is expected to be higher in cardiovascular patients [8,9]. Patient-related characteristics such as disease's nature, comorbidities and the state of patient's renal and hepatic functions could be a factor. Certain cardiovascular drug features can raise the risk of pDDIs, notably having a narrow therapeutic index, a cytochrome P450 (CYP450) substrate/inhibitor/inducer; P-glycoprotein (P-gp) substrate/inhibitor/inducer; an OATP transport protein substrate or a known QT_c interval prolonging agent [3,8]. Numerous cardiovascular drugs can induce iatrogenic cardiac illnesses such as diuretics which could cause hypo- or hyperkalemia or ACEIs (angiotensin converting enzyme inhibitors) that could induce precipitate acute renal failure [10].

Checking and managing DDIs requires the assistance of computerised KBs. It's difficult for practitioners or pharmacists to identify all pDDIs in prescriptions particularly those with polypharmacy [11]. Nevertheless, KBs differ significantly in the number and risk rating of recognized pDDIs. Many pDDIs identified by KBs can be of low clinical reliability, increasing the physician's burden (alert fatigue) which could lead to ignoring other clinically significant pDDIs (alert override) [9,12].

The objectives of this study were to recognize the frequency and risk factors of pDDIs in prescriptions of cardiovascular hospitalised patients using three KBs; Lexicomp®, Micromedex® and the free Drug Interactions Checker®, and to compare the inclusion and gradings of pDDIs in these KBs. We highlight some clinically significant cardiac pDDIs with appropriate monitoring options.

2. METHODS

2.1 Study Design and Setting

A cross-sectional observational study was conducted in the cardiology department and its ICU of Assiut University Hospitals from September 2013 to October 2014. This is one of the largest academic medical institutions in Egypt that serves all Upper Egypt's governorates. The study was approved by the Research Ethics Committee at the Faculty of Medicine of Assiut University.

2.2 Study Population

The study included 125 patients admitted to the cardiology ward and to ICU of the department. Only patients' prescriptions with two or more drugs prescribed during hospitalization were included in the study. All age ranges, drug groups, and comorbidities were included.

2.3 Data Collection

Data were collected manually from the patients' medication orders. The department lacks a Computerized Physician Order Entry (CPOE) system thus, it was not possible to access data or screen for pDDIs automatically. In hospital wards, all patient's medical information is handwritten in medication charts. Therefore we developed, a medication checklist for easy collection and handling of patients' data. No specific KB is preferred or mandated by the department. Hence, clinical pharmacists check for pDDIs by entering each one of the medications into a free drug interaction checker simultaneously to identify the quantity and severity of pDDIs.

Each patient's medication list was screened for pDDIs using three electronic KBs; Lexicomp®, Micromedex® and Drug Interactions Checker® by Cerner Multum™ at Drugs.com® to compare these KBs regarding inclusion and grading of pDDIs. All medications in the patients' prescriptions including nutraceuticals (dietary supplements) were included in the pDDIs check. For statistical analysis of patients' data, pDDI results from the Lexicomp® were used. In Lexicomp®, each pDDI is assigned a grading of A, B, C, D or X [13]. Since A and B gradings are of academic but not clinical concern, they were not accounted for in statistical analysis. The grading classifications of the three KBs are defined in Supplementary Table(S1).

2.4 Statistical Analysis of Data

All collected and extracted data were statistically analyzed using Statistical Package for Social Science (SPSS) version 22.0. The total sample size was calculated based on a 95% confidence level, a 5% probability of alpha error and power of 80%. Categorical data were expressed as frequencies and percentages while continuous data were expressed as mean± standard deviation. The factors predicting the number of pDDIs on admission were estimated by multiple linear regression using robust standard errors. Spearman's rank-order correlations with bootstrapped confidence intervals were carried out to measure the strength and direction of the association between two continuous variables. The Mann–Whitney U non-parametric test was used for comparisons when the t test did not meet the usual assumptions of normality and homoscedasticity. Comparisons between categorical variables were performed using the chi-square test of association or Fisher's Exact test whenever appropriate. Binary logistic regression was performed to calculate the odds ratios for risk estimation. Statistical significance was defined as p-value<0.05.

To assess inclusion of clinically significant pDDIs in the three KBs, we consulted the "high priority" DDIs list developed by the United States Office of the National Coordinator for Health Information Technology [14] and the list of 15 common pDDIs provided by CredibleMeds® which emphasizes evidenced pDDIs of cardiovascular medications [15].

3. RESULTS

3.1 Patient Characteristics

During the study period, 125 patients with at least one prescription with two medications were recorded. Table 1 shows the patients' demographics and clinical characteristics. Just over a quarter of the patients aged above 65 (N=33, 26.4%) of which 32 (96.96%) had an order of five drugs or more. In fact, about 85.9% (N=79) of the patients who were younger than 65 were also prescribed five or more drugs from a total of 133 different medications. Ninety-six percent (N=120) of the patients were treated for at least two health conditions.

Table 1. Demographics and clinical characteristics of patients (N=125)

Sex N (%)	Male Female	63 (50.4%) 62 (49.6%)
Age (years)	Range Mean ± SD	20-86 53.57 ± 15.26
Length of hospital stay	Range Mean ± SD	2-26 8.98 ± 4.25
Drugs prescribed	Range Mean ± SD	2-20 8.1 ± 3.57
Clinical diagnosis N (%)	Cardiomyopathy Congestive Heart Failure Ischemic Heart Disease Rheumatic Heart Disease Atrial Fibrillation Myocardial Infarction	33 (26.4%) 30 (24%) 29 (23.2%) 27 (21.6%) 25 (20%) 14 (11.2%)
Comorbidities N (%)	Diabetes Hypertension Anemia Chest Infection Renal Impairment Liver disease Hepatitis C	32 (25.6%) 29 (23.2%) 21 (16.8%) 13 (10.4%) 12 (9.6%) 8 (6.4%) 3(2.4%)

3.2 Potential Drug-Drug Interactions from Lexicomp®

Upon analysis of prescriptions, a sum of 1069 pDDIs were found which resulted from 224 unique drug combinations. Table 2 displays recurrence of C, D and X DDIs among cardiac patients and the most common pDDI pairs found in this study are presented in the supplementary Table (S2). Drug classes mostly prescribed were antithrombotics, antiarrhythmics, diuretics, and ACEIs. Low-dose aspirin, digoxin, furosemide and ramipril were the most widely used agents representing those classes, respectively. While aspirin represented (48%) of total prescribed antithrombotics, enoxaparin constituted (29.6%), clopidogrel (24%) and warfarin (23.2%). Table 3 shows ordered combinations of low-dose aspirin with other antithrombotics. Nutraceuticals were ordered in prescriptions of 20 patients and included oral iron preparations, milk thistle, multivitamins, calcium and Ginkgo biloba.

Table 2. The distribution of different types of pDDIs

Total pDDIs= 1069, Total Unique pDDIs Pairs= 224		
Type C pDDI	Total number of C DDI, N (%)	932 (87.2%)
	Total number of C DDI, N (%) per Total pDDIs Pairs	177 (79%)
	Mean± SD/Patient	7.45 ± 6.69
	Minimum, Maximum/Patient	0 – 39
	Patients, N (%) with at least one interaction	121 (96.8%)
Type D pDDI	Total number of D DDI, N (%)	106 (9.9%)
	Total number of D DDI, N (%) per Total pDDIs Pairs	34 (15.2%)
	Mean± SD/Patient	0.85 ± 1.45
	Minimum, Maximum/Patient	0 – 10
	Patients, N (%) with at least one interaction	51 (40.8%)
Type X pDDI	Total number of X DDI, N (%)	31 (2.9%)
	Total number of X DDI, N (%) per Total pDDIs Pairs	13 (5.8%)
	Mean± SD/Patient	0.25 ± 0.5
	(Minimum, Maximum)/Patient	0 – 2
	Patients, N (%) with at least one interaction	27 (21.6%)

Thirty of the patients (24%) were treated with the potentially significantly nephrotoxic triple combination of ACE inhibitors/ARA (angiotensin receptor antagonists), diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs). An ACEI was used more than (73.3%) an ARA in this combination. The majority of those patients (N=24/80%) was over age 50. In addition, 21 (70%) patients had high levels of both serum creatinine (SCr) and blood urea nitrogen (BUN), while 7 patients had only elevated BUN levels. Table 4 shows normal BUN and SCr values used by the hospital's laboratory for renal function evaluation, and their descriptive values in patients on triple therapy.

3.3 Risk Factors for Potential Drug Interactions

Statistical analysis of data by multivariate regression with robust standard errors has shown that age, sex, length of hospital stay and comorbidities had no impact on the number of pDDIs (p=0.83, 0.51, 0.62, 0.87 respectively). Contrarily, the number of drugs prescribed per patient could significantly predict the number of pDDIs, (p<0.001). The model accounted for 74% of the explained variability in the number of pDDIs. For every additional drug in a prescription there was an expected increase of 2.1 pDDIs. A Spearman's correlation with bootstrapping has also confirmed that the number of drugs is a strong predictor of pDDIs (r_s(123)=0.808; bias-corrected and accelerated [BCa] 95%CI, 0.719–0.873; p<0.001), and a weak positive correlation appeared between age and pDDIs (r_s(123)=0.231; bias-corrected and accelerated [BCa] 95%CI, 0.061–0.387; p=0.009). A positive association was found between the length of hospital stay and pDDIs (r_s(123)=0.376; bias-corrected and accelerated [BCa] 95%CI, 0.210–0.531; p<0.001). Furthermore, a moderate positive correlation was demonstrated between the number of comorbidities and pDDIs (r_s(123)=0.493; bias-corrected and accelerated [BCa] 95%CI, 0.339–0.619; p<0.001).

Scores of pDDIs for hospital stay of seven days or more (mean rank=69.99) were significantly higher than for those under seven days (mean rank=46.99), U=2261.5, z=3.272, p=0.001. The same was true for scores of pDDIs in presence (mean rank=71.79) versus absence (mean rank=36.35) of comorbidities, U=2283, z=4.731, p=0.001.

Given the very high prevalence of pDDI (~97%) in the study, possible risk factors were analyzed at higher thresholds (pDDI≥7; pDDI≥15) using both Chi-square test and binomial logistic regression with 95% confidence intervals. Therefore, continuous predictor variables were dichotomized at the median value. Factors included age 55 and older, orders of seven or more drugs, hospitalization of seven days or more, presence of three or more comorbidities, and patient orders including CYP450 inhibitors or inducers. Analyses results are shown in Table 5.

Table 3.

Frequency of low-dose aspirin combinations with other antithrombotics	N (%)
Aspirin alone	22 (36.7)
Aspirin + Clopidogrel + Enoxaparin	21 (35)
Aspirin + Clopidogrel	6 (10)
Aspirin + Warfarin	5 (8.3)
Aspirin + Enoxaparin	4 (6.7)
Aspirin + Clopidogrel + Warfarin	1 (1.7)
Aspirin + Clopidogrel + Enoxaparin + Warfarin	1 (1.7)

Table 4.

a. Normal laboratory reference ranges used to evaluate the level of renal function		
	BUN mmol/ L	**Serum creatinine µmol/L**
Male	2.5-6.4	55-127
Female		45-100
b. Values in patients on "triple whammy"		
Mean ± SD	14.36 ± 6.6	147.3 ± 54.0
Range	6.1-29.6	79.7-327.4

Table 5. Factors associated with the rate of potential DDIs in the cardiology department

Predictive factors	pDDIs ≥ 7[†]			pDDIs ≥ 15[‡]		
	Beta (SE)	**OR (95% CI)**	***p* value**	**Beta (SE)**	**OR (95% CI)**	***p* value**
Age ≥55	.31 (.49)	1.36 (.52-3.58)	.004 [§]	-.19 (.6)	.82 (.25-2.67)	.124[§]
Drugs ≥7	2.14 (.54)	8.57 (2.95-24.68)*	< .001[§]	ND	ND	< .001[§]
Hospital Stay ≥7	-.28 (.54)	.75 (.26-2.18)	.052[§]	1.22 (.85)	3.39 (.647-17.74)	.003[§]
Comorbidities ≥3	.56 (.49)	1.74 (.66-4.62)	.006[§]	-.45 (.57)	.96 (.312-2.93)	.167[§]
Cytochrome P450 Inhibitors	1.61 (.49)	5.02 (1.9-13.26)*	< .001[§]	1.77 (.72)	5.54 (1.36-22.48)*	< .001[§]
Cytochrome P450 Inducers	1.3 (.94)	3.67 (.58-23.08)	< .001[§]	.75 (.6)	2.11 (.65-6.89)	.001[¶]

[†]R^2: 0.375 (Cox & Snell), 0.501 (Nagelkerke). Model $\chi 2(6) = 58.67$, $p < .001$.
[‡]R^2: 0.291 (Cox & Snell), 0.449 (Nagelkerke). Model $\chi 2(6) = 42.99$, $p < .001$.
**p< 0.001, [§]: Chi-square test; [¶]: Fisher's exact test.*
ND: not determined because all patients in the study treated with <7 drugs had <15 pDDIs
SE: Standard error. OR: Odds ratio. CI: Confidence interval

Hospital stay of seven days and over was significantly correlated with having 15 pDDIs or more [$\chi2(1)=8.61$, $\varphi=0.262$, $p=.003$]. There was a moderately strong association between encountering seven or more pDDIs in patients treated for three or more medical conditions [$\chi2(1)=7.62$, $\varphi=0.247$, $p=.006$]. Additionally, having three or more comorbidities was positively associated with having a contraindicated type X pDDI [$\chi2(1)=5.07$, $\varphi=0.201$, $p=.024$]. A connection between the occurrence of seven or more pDDIs and CYP450 inhibitors was found to be of very strong statistical significance, [$\chi2(1)=23.9$, $\varphi=0.437$, $p<.001$]. While there was a strong association with the presence of CYP450 inducers [$\chi2(1)=12.7$, $\varphi=0.319$, $p<.001$].

Regarding the "triple whammy", there was a strong statistically significant relationship between cases medicated with the triple therapy and having high levels of SCr [$\chi2(1)=11.55$, $\varphi=0.304$, $p=.001$] and BUN [$\chi2(1)=16.97$, $\varphi=0.368$, $p<.001$].

3.4 Comparison of Knowledge Bases

The size of the KBs varied in terms of identified drug pairs and there was a slight variation in the inclusion of drugs among the three KBs. All drugs prescribed in the cardiovascular department during this study were recognized by Lexicomp® while ten drugs were not found in Drugs.com®. Those included betahistine, bromhexine, mosapride, nicorandil, nimesulide, piracetam, teicoplanin, tenoxicam, trimebutine and trimetazidine. Although nimesulide and tenoxicam were absent in Drugs.com®, representatives of the NSAIDs class were present (ibuprofen and ketorolac). Only two drugs were not recognized by Micromedex®; mosapride and nicorandil.

Counting all gradings of pDDIs, Drugs.com® alerted the largest number of pDDIs at a total of 1227, followed by Lexicomp® which recognized 1219 pairs. Micromedex® identified only 876 pDDIs. Consequently, the median and range of pDDIs in all patients followed the same order. They were 8 (range:0–63), 7 (range:0–56) and 6 (range:0–44) for Drugs.com® Lexicomp® and Micromedex®, respectively.

Both Drugs.com® and Lexicomp® have shown that most prevalent pDDIs were moderate and that contraindicated were the least, while the major grading was the largest in Micromedex®. The number of distinct pDDIs per grading of the three KBs are shown in Table 6. Micromedex rated only the combined use of NSAIDs as contraindicated.

Jointly, the KBs predicted 697 distinct drug pairs, of which 115 were in all three KBs Fig. 1. There was a disagreement in the rating of DDIs among the three KBs. Of the 115 DDI pairs identified by all three KBs, there was agreement on the grading of only 38. Ten of those pDDIs were rated as major, 27 as moderate and one as minor as listed in supplementary Table (S3). The highest agreement on inclusion (24.8%) and rating (56%) of pDDIs was between Drugs.com® and Lexicomp®.

Comparing only drug pairs found in this study, the three KBs included the candidate drug pair #25 from the "high-priority" list as a pDDI of major risk. During our study, simvastatin and amiodarone were co-prescribed. Despite atorvastatin was omitted from the interacting class due to reduced risk, the three KBs still alerted the use of atorvastatin with clarithromycin and diltiazem as major pDDIs.

Eight out of the 15 pDDIs in the list of CredibleMeds® were in all three KBs. Those were; amiodarone and quinolones, digoxin and macrolides, simvastatin and amiodarone, and warfarin with amiodarone, fibrates, NSAIDs, statins and antibiotics. The remaining pairs were not prescribed in patients' records during the study period.

Table 6. Number of DDIs per database for the different risk rating categories

Risk rating	Knowledgebase		
	Micromedex®	Lexicomp®	Drugs.com®
Contraindicated	1	13	-
Major	81	34	44
Moderate	65	177	193
Minor	12	18	22

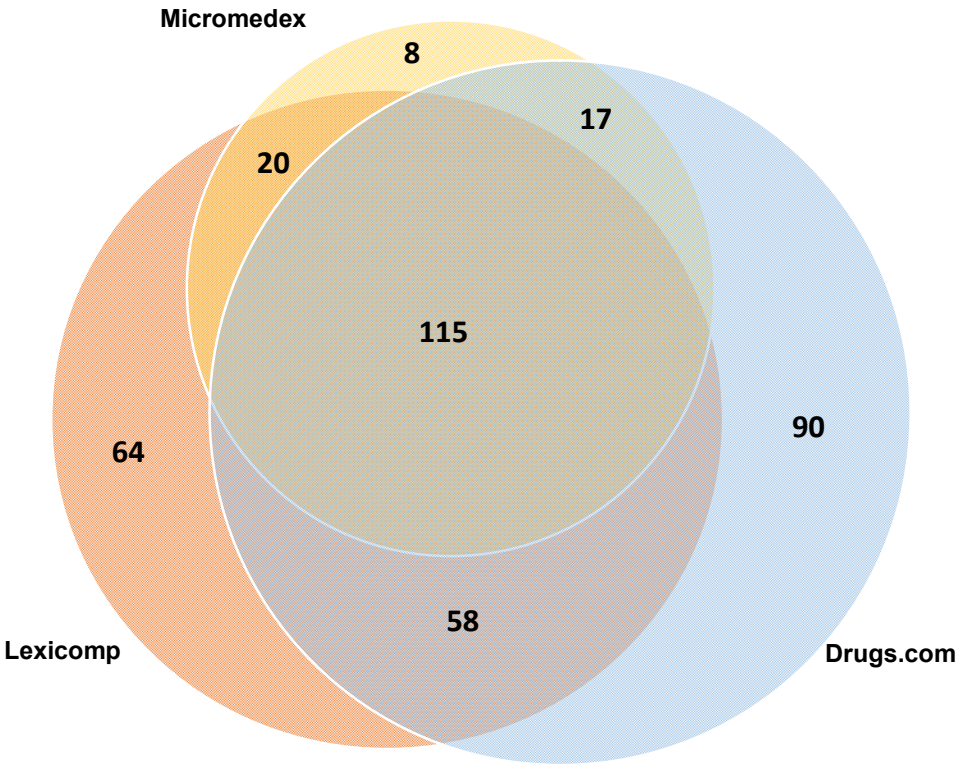

Fig. 1. Overlap of pDDIs between the knowledge bases diagram produced by Venn diagram Plotter, version 1.5.5228.29250

4. DISCUSSION

Cardiovascular drugs carry a higher risk for pDDIs. In a recent study, cardiovascular agents were found to be the therapeutic class predominantly altered by co-medications [16]. Our study uncovered a very high prevalence of pDDIs (96.8%) compared to that disclosed in other studies which ranged from 35.5-83.9% [17-19]. Another study which was similarly carried at a cardiology department of a teaching hospital for a one year period, had a close prevalence of 91.6% [20]. All prescriptions with pDDIs had at least one type C pDDI, except for one which had one pDDI of type X. This higher percentage of pDDIs in our investigation can be a result of various study designs, different pDDIs screening tools, the absence of a computerized alert system and diverse hospital settings. Fortunately, the services of clinical pharmacy have been integrated in various departments in Egyptian hospitals and its role is growing more influential which may partially compensate for alert systems.

Our results show a solid relationship between the number of medications and the likelihood of pDDIs which are in accordance with several previous studies [17,19,20]. Age was not a risk factor among the population of this study probably because most patients (88.8%) were treated with five or more drugs. Positive correlations of varying strengths were detected between pDDIs and the number of drugs, length of hospital stay and number of comorbidities. A new study of warfarin-drug interactions at the same cardiovascular department has comparably described positive correlations with all three factors [21].

The association between hospital stay of seven days and over and having 15 pDDIs or more, could be a result of adding more drugs to the prescription order during extended hospitalization. This was observed in consecutive daily prescriptions, where medications were changed or stopped, and more were added. Such outcome compares well with other literature reports although carried under dissimilar settings. Previous studies have deduced that prolonged

hospital stay is linked to modifying medications and subsequent increase in pDDIs [20,22].

An additional risk factor for pDDIs was comorbidities, which conforms with the fact that patients suffering from multiple illnesses, require an intricate treatment plan of different drug classes.

Since each CYP isoform can metabolize a wide range of substrates, alterations in the metabolism of CYP450 enzymes are the cause of numerous pharmacokinetic DIs [3]. Amiodarone and ciprofloxacin were the most often prescribed CYP inhibitors. Both are potent CYP1A2 inhibitors. Amiodarone also being a CYP2C9 and CYP2D6 potent inhibitor and a highest risk QT_c-prolonging agent, imposes further risk for DDIs and consequently serious ADRs [23]. The mechanism of more than 25% of total amiodarone pDDIs in this study was CYP mediated.

Among assessed potent inducers were phenobarbitone, phenytoin and rifampin. Positive correlations between pDDIs and both CYP450 inducers and inhibitors at the time of hospital discharge were found previously in the literature [24], which analyzed risks for pDDIs at an ICU at different hospital stay points.

The pDDI informally known as the “triple whammy”, was investigated. Nephrotoxic effects are caused by diverse complex mechanisms leading to volume depletion. They specifically affect elderly patients, and those with cardiovascular conditions like chronic heart failure and chronic renal failure (CRF) [25].

Elevated levels of SCr and BUN noticed in patients’ lab test results, possibly signal an altered kidney function. Moreover, five of those patients were diagnosed with renal impairment or CRF. However, patients with cardiovascular conditions have numerous predisposing factors that can increase serum creatinine, including excessive diuresis, nephrotoxicity of medications, diagnostic media and disease-induced renal impairment [26]. In consequence, future attempts should be considered to differentiate causality based on the timeline of presentation or mechanism. Details of different prescribed “triple therapy” combinations are presented in the supplementary table (S4). This combination is of concern essentially that NSAIDs are accessible over-the-counter, and the combination of an ACEI/ARA and one or more diuretic are routinely co-prescribed or sold as a single pill for treatment of hypertension and congestive heart failure (CHF) [27]. This dual therapy, which has also been referred to as the “double whammy” was prescribed for 20 other patients of the current study. The “double whammy” has been reported to hold a similar risk for acute kidney failure as the “triple whammy”. The benefit of such combinations versus their nephrotoxic risk should be singly weighed prior to a prescription decision [28,29]. If the combination was deemed unavoidable, SCr and electrolyte levels should be monitored closely. Prescribers should be necessarily alert for signs of illness particularly dehydration and orthostatic hypotension or initiation of an NSAID. If patients are to be discharged on the “double whammy”, they should be educated on the careful use of NSAIDs with immediate reporting of any signaling symptoms of renal toxicity [28]. Most frequently prescribed type C pDDI was digoxin with loop diuretics, an interaction of fair reliability. Loop diuretics can result in hypokalemia and hypomagnesemia and increased cardiac glycoside toxicity. Therefore, observation of potassium and magnesium levels, and replacement of losses is recommended [30].

Although the combined use of ACEI/ARA with potassium-sparing diuretics (a type C pDDI flagged in 28.8% of prescriptions) is a standard practice for treating patients with severe CHF, the risk of life-threatening hyperkalemia has been reported [31,32]. It is judicial to promptly observe potassium levels after starting this combination. Monitoring recommendations include wise selection of ACEI/ARA doses, addition of a thiazide or loop diuretic, and watching renal function and diet [31-33].

A sum of 51 patients had encountered pDDIs of type D risk. Type D comprised 8.8% of total pDDIs, matching a study findings in an Iranian teaching hospital [17]. Whereas this percentage was slightly higher compared to a study of hospitalized patients in Slovenia [34]. Researchers in both studies used Lexicomp®.

An exemplar of type D pDDIs was that between clopidogrel and proton pump inhibitors (PPIs). Clopidogrel is the most broadly used antiplatelet for management of myocardial infarction and stroke. PPIs which are moderate CYP2C19 inhibitors, are given jointly to protect against gastrointestinal bleeding in high-risk patients receiving long-term antiplatelet therapy [35]. Clopidogrel, a prodrug, is an irreversible inhibitor of P2Y12 receptor and requires metabolic

activation by CYP450. The attenuated antiplatelet effect was reported to be more prominent with omeprazole or esomeprazole than with other PPIs such as dexlansoprazole or lansoprazole [36]. Pantoprazole or H_2 blockers may be considered as alternative gastroprotective agents. Considering ongoing research, treatment regimens should be tailored to individual patient's medical status and cardiovascular risks [35,36].

One of type X pDDI noted in this study was the co-prescription of amiodarone and sulpiride. Class III antiarrhythmic agent amiodarone, is effective in the treatment of severe rhythm disorders [37]. Yet, amiodarone can cause multiple cardiac and non-cardiac ADRs, including bradycardia, QT interval prolongation, and possible development of torsades de pointes (TdP) [37,38]. Sulpiride as many antipsychotics is also known to be associated with a long QT_c interval on ECG and TdP [38]. Another contraindicated pDDI was clarithromycin with amiodarone. Macrolide antibiotics may induce cardiotoxicity on their own and thus the risk can be seriously augmented if used with other drugs known to prolong the QT_c interval or initiate TdP. Establishing tailored protocols in hospitals to monitor QT measurements is, therefore, a vital requisite [39].

Any OTC products that were potentially used by the patient without a medical prescription were not included as they are not recorded in medication orders or patient's history. Nonetheless, some nutraceuticals were ordered in 16% of the prescriptions and were involved in pDDIs ranging from minor to major severity. One example was the co-prescription of Gingko biloba and warfarin which could increase the risk of bleeding. Dietary supplements should not always be thought of as harm-free and their use should be evaluated particularly in patients receiving multiple drugs [40].

Several studies had concluded that there is minimal agreement, either on inclusion or grading of pDDIs among commonly used drug interaction KBs [9,11,41]. The three KBs compared in this study agreed on inclusion of only 16.5% of the distinct interacting pairs and 33% of grading. Although ten drugs were absent in Drugs.com®, the database produced the highest number of pDDIs alerts. In the absence of a standard alerting system and as a popular freely accessible KB, clinical pharmacists at the cardiovascular department use it most. All pDDIs found in Drugs.com® only, were either of moderate or minor severity which should not increase concern but could be consulted in case of actual ADRs. Drugs.com® included all interactions in the 'high-priority" and CredibleMeds lists with the same grading as both Lexicomp® and Micromedex®. A prospective study compared the same three KBs against probable clinically relevant DDIs [9], and has shown that Drugs.com® had the highest specificity, an equal positive predictive value to that of Micromedex®, but it had the least sensitivity. The positive predictive value of Drugs.com® and Micromedex® was much higher than that of Lexicomp® however, they all yielded the same high negative predictive values. Therefore, when using Drugs.com® as a source for checking pDDIs when other paid databases are inaccessible through the institution, it's necessary to identify pDDIs of highest clinical risk. Excessive alerting is burdensome to clinicians, particularly when minor or moderate interactions are included [42]. Such a burden could lead the physicians to override true positive alerts [12]. Accordingly, until standardized protocols and alert systems are set, such variation among different KBs should be well-considered.

5. LIMITATIONS

This study is considered the first in Assiut University Hospital to cover the prevalence and causation of pDDIs. It opens the way for further research in an attempt to unveil other sources of ADRs and to monitor health services' quality.

Limitations of this study were the study design and the small number of patients. During the study, recommendations were only provided in a few cases on physician's demand. However, detailed suggestions and management options were supplied for the department after the investigation. Frequency of pDDIs was based on the used database and not actual ADRs or patient complaints. This specific approach can be conducted in new studies. Analyzing more prescriptions would have been more accessible with computerized databases. Another limitation can be that possible OTC medications and herbal remedies were not included in screening.

6. CONCLUSION

This investigation has revealed a very high prevalence of pDDIs in patients admitted to the cardiovascular department and ICU of Assiut University Hospitals. Polypharmacy was a major

risk factor. Other factors included a length of hospital stay, comorbidities and features of prescribed drugs.

Following identification of pDDIs, the clinician should assess potential risks and benefits of adding any new medication to the regimen of a complex cardiovascular patient with multiple comorbidities and underlying polypharmacy. The collaboration of pharmacists, in conjunction with development and integration of computerized databases that would be periodically evaluated, can positively impact prescribing practices.

Implementation of medication review algorithms and plans to reduce ADRs and medication errors is required. Due to the substantial variability among KBs, the health team needs to determine the most relevant approach to check for DDIs while balancing between avoiding excessive alerting and overriding significant interacting drug pairs. Auditing cycles are important after enacting tailored guidelines to analyze limitations and optimize outcomes.

CONSENT

As per international standard or university standard written participant consent has been collected and preserved by the authors.

ETHICAL APPROVAL

The study was approved by the Research Ethics Committee at the Faculty of Medicine of Assiut University.

COMPETING INTERESTS

The authors declare that there is no competing interest.

REFERENCES

1. Palleria C, Di Paolo A, Giofrè C, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences. 2013;18(7):601-10.
2. Casuccio A, Ferrante M, Scondotto G, et al. Hospitalization and mortality among the elderly exposed to polytherapy and at risk of adverse drug reactions. Giornale Italiano di Farmacia Clinica. 2017;31:16-22.
3. Kennedy C, Brewer L, Williams D. Drug interactions. Medicine. 2016;44(7):422-6.
4. Gallelli L, Siniscalchi A, Palleria C, et al. Adverse drug reactions related to drug administration in hospitalized patients. Curr Drug Saf. 2017;12(3):171-7.
5. Ansari J. Drug interaction and pharmacist. J Young Pharm. 2010;2(3):326-31.
6. Vlahović-Palčevski V, Mentzer D. Postmarketing surveillance. In: Seyberth HW, Rane A, Schwab M, editors. Pediatric Clinical Pharmacology. Berlin, Heidelberg: Springer Berlin Heidelberg; 2011. p. 339-51.
7. Weiler S, Kullak-Ublick GA, Jetter A. [Tips for practice: Clinically relevant adverse drug interactions]. Switzerland Med Forum. 2015;15(07):152-6.
8. Wiggins BS, Saseen JJ, Page RL, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: A scientific statement from the American heart association. Circulation. 2016;134: e468–e95.
9. Muhic N, Mrhar A, Brvar M. Comparative analysis of three drug-drug interaction screening systems against probable clinically relevant drug-drug interactions: A prospective cohort study. Eur J Clin Pharmacol. 2017;73(7):875-82.
10. Darchy B, Le Mière E, Figuérédo B, et al. Iatrogenic diseases as a reason for admission to the intensive care unit: Incidence, causes, and consequences. Arch Intern Med. 1999;159(1):71-8.
11. Fung KW, Kapusnik-Uner J, Cunningham J, et al. Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support. J Am Med Inform Assoc. 2017;24(4):806-12.
12. Wipfli R, Lovis C. Alerts in clinical information systems: building frameworks and prototypes. Stud Health Technol Inform. 2010;155:163-9.
13. Lexicomp-Online®. Lexicomp® Interactions Module. Hudson, Ohio: Lexi-Comp, Inc.; [cited 2017 March]. Available:http://online.lexi.com/lco/action/interact.
14. Phansalkar S, Desai AA, Bell D, et al. High-priority drug–drug interactions for use in electronic health records. Journal of the

American Medical Informatics Association: JAMIA. 2012;19(5):735-43.

15. CredibleMeds. Clinically Important, Common Drug-Drug Interactions (DDIs) [cited 2018 May]. Available:https://crediblemeds.org/healthcare-providers/drug-drug-interaction/.
16. Hanlon JT, Perera S, Newman AB, et al. Potential drug-drug and drug-disease interactions in well-functioning community-dwelling older adults. J Clin Pharm Ther. 2017;42(2):228-33.
17. Namazi S, Pourhatami S, Borhani-Haghighi A, et al. Incidence of Potential Drug-Drug Interaction and Related Factors in Hospitalized Neurological Patients in two Iranian Teaching Hospitals. Iran J Med Sci. 2014;39(6):515-21.
18. Ismail M, Aziz S, Noor S, et al. Potential drug-drug interactions in pediatric patients admitted to intensive care unit of Khyber Teaching Hospital, Peshawar, Pakistan: A cross-sectional study. J Crit Care. 2017;40:243-50.
19. Kovacevic M, Vezmar Kovacevic S, Miljkovic B, et al. The prevalence and preventability of potentially relevant drug-drug interactions in patients admitted for cardiovascular diseases: A cross-sectional study. Int J Clin Pract. 2017;e13005.
20. Murtaza G, Khan MY, Azhar S, et al. Assessment of potential drug-drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharm J. 2016;24(2):220-5.
21. Abdel-Aziz MI, Ali MA, Hassan AK, et al. Warfarin-drug interactions: An emphasis on influence of polypharmacy and high doses of amoxicillin/clavulanate. J Clin Pharmacol. 2016;56(1):39-46.
22. Moura CS, Acurcio FA, Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. J Pharm Pharm Sci. 2009;12(3):266-72.
23. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician. 2007;76(3): 391-6.
24. Reis AM, Cassiani SH. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. Clinics (Sao Paulo). 2011;66(1): 9-15.
25. Bryant BJ, Knights KM. Pharmacology for Health Professionals. 4th ed. Chatswood, New South Wales: Elsevier Australia; 2015.
26. Pazhayattil GS, Shirali AC. Drug-induced impairment of renal function. Int J Nephrol Renovasc Dis. 2014;7:457-68.
27. Boarder M, Dixon J, Newby D, et al. Pharmacology for pharmacy and the health sciences: A patient-centred approach. 2nd ed. Oxford: Oxford University Press; 2017.
28. Garcia Camin RM, Cols M, Chevarria JL, et al. Acute kidney injury secondary to a combination of renin-angiotensin system inhibitors, diuretics and NSAIDS: "The Triple Whammy". Nefrología (English Edition). 2015;35(2):197-206.
29. Prieto-Garcia L, Pericacho M, Sancho-Martinez SM, et al. Mechanisms of triple whammy acute kidney injury. Pharmacol Ther. 2016;167:132-45.
30. Wang MT, Su CY, Chan AL, et al. Risk of digoxin intoxication in heart failure patients exposed to digoxin-diuretic interactions: a population-based study. Br J Clin Pharmacol. 2010;70(2):258-67.
31. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA. 2003;289(13):1652-8.
32. Fujii H, Nakahama H, Yoshihara F, et al. Life-threatening hyperkalemia during a combined therapy with the angiotensin receptor blocker candesartan and spironolactone. Kobe J Med Sci. 2005;51(1-2):1-6.
33. Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cardiovasc Ther. 2012;30(3): e156-66.
34. Roblek T, Trobec K, Mrhar A, et al. Potential drug-drug interactions in hospitalized patients with chronic heart failure and chronic obstructive pulmonary disease. Arch Med Sci. 2014;10(5):920-32.
35. Bouziana SD, Tziomalos K. Clinical relevance of clopidogrel-proton pump inhibitors interaction. World J Gastrointest Pharmacol Ther. 2015;6(2):17-21.
36. Hariharan S, Southworth MR, Madabushi R. Clopidogrel, CYP2C19 and proton pump inhibitors: What we know and what it means. The Journal of Clinical Pharmacology. 2014;54(8):884-8.

37. Siddoway LA. Amiodarone: Guidelines for use and monitoring. Am Fam Physician. 2003;68(11):2189-96.
38. Brouillette J, Nattel S. A practical approach to avoiding cardiovascular adverse effects of psychoactive medications. Can J Cardiol. 2017;33:1577-86.
39. Guo D, Cai Y, Chai D, et al. The cardiotoxicity of macrolides: A systematic review. Die Pharmazie - An International Journal of Pharmaceutical Sciences. 2010;65(9):631-40.
40. Russo R, Gallelli L, Cannataro R, et al. When nutraceuticals reinforce drugs side effects: A case report. Curr Drug Saf. 2016;11(1):1-3.
41. Vitry AI. Comparative assessment of four drug interaction compendia. Br J Clin Pharmacol. 2007;63(6):709-14.
42. Malone D. Individualized drug interaction alerts - Final report. (Prepared by the University of Arizona under Grant No. R21 HS023826). Rockville, MD: Agency for Healthcare Research and Quality; 2017.

Supplementary Table S1

Lexi-Interact®, Drug-Reax® and Drug Interactions Checker® drug-drug interaction classifications					
Lexi-Interact® Risk rating		Drug-Reax® Risk rating		Drug Interactions Checker® Risk rating	
A No known Interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions	Unknown	Unknown	Unknown	No information available.
B No action needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.	Minor	The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a Major alteration in therapy.	Minor	Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.
C Monitor therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients	Moderate	The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy.	Moderate	Moderately clinically significant. Usually avoid combinations; use it only under special circumstances.

Supplementary Table S1. *continued*

Lexi-Interact® Risk rating		**Drug-Reax® Risk rating**		**Drug Interactions Checker® Risk rating**	
D Consider therapy modification	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.	**Major**	The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects.	**Major**	Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.
X Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.	**Contra-indicated**	The drugs are contraindicated for concurrent use.		

Supplementary Table S2

Frequency of the most common pDDIs Interactions	Rate/ 125 patients (%)
Type C (Monitor therapy)	
Digoxin + Loop Diuretics (furosemide/ torsemide/ bumetanide)	42 (33.6%)
ACE Inhibitors (captopril/ enalapril/ lisinopril/ perindopril/ ramipril) + Loop Diuretics	39 (31.2%)
ACE Inhibitors + Aspirin	36 (28.8%)
Aspirin + Loop Diuretics	36 (28.8%)
Amiodarone + Loop Diuretics	34 (27.2%)
Loop Diuretics + Insulin & Oral Antidiabetics (glimepiride/ glyburide/ metformin)	32 (25.6%)
Aspirin + Clopidogrel	30 (24%)
ACE Inhibitors + Potassium-sparing diuretics (amiloride/ spironolactone)	29 (23.2%)
Digoxin + Potassium-sparing diuretics	29 (23.2%)
Aspirin + Enoxaparin	26 (20.8%)
ACE Inhibitors + Enoxaparin	22 (17.6%)
Amiodarone + Potassium-sparing diuretics	22 (17.6%)
Aspirin + Insulin & Oral Antidiabetics	22 (17.6%)
ACE Inhibitors + Nitroglycerin	18 (14.4%)
Albuterol + Loop Diuretics	18 (14.4%)
Amiodarone + ACE Inhibitors	16 (12.8%)
Loop Diuretics + Ivabradine	15 (12%)
Amoxicillin/ Clavulanate + Warfarin	12 (19.6%)
Amiodarone + Clopidogrel	9 (7.2%)
Enoxaparin + Potassium-sparing diuretics	8 (6.4)
ARA (candesartan/ olmesartan/ valsartan) + Potassium-sparing diuretics	7 (5.6%)
Warfarin + Ciprofloxacin/ Levofloxacin/ Norfloxacin/ Ofloxacin	7 (5.6%)
Loop Diuretics + Gentamicin	7 (5.6%)
Type D (Modify regimen)	
Amiodarone + Warfarin	14 (11.2%)
Amiodarone + Digoxin	13 (10.4%)
Potassium-sparing diuretics + Potassium chloride	12 (19.6%)
Albuterol + Amiodarone	7 (5.6%)
Aspirin + Warfarin	7 (5.6%)
Clopidogrel + Proton Pump Inhibitors (omeprazole/ pantoprazole)	6 (4.8%)
Loop Diuretics + NSAIDs (aspirin/ ibuprofen/ ketorolac/ nimesulide/ tenoxicam)	6 (4.8%)
Magnesium sulfate + Levofloxacin/ Norfloxacin/ Ofloxacin	4 (3.2%)
Aminophylline/ Theophylline + Norfloxacin/ Ofloxacin	3 (2.4%)
Aminophylline/ Theophylline + Midazolam	2 (1.6%)
Amiodarone + Metronidazole	2 (1.6%)
Type X (Avoid combination)	
Amiodarone + Ciprofloxacin/ Levofloxacin/ Ofloxacin	6 (4.8%)
Amiodarone + Ivabradine	3 (2.4%)
Albuterol + Carvedilol/ Propranolol	3 (2.4%)
Amiodarone + Sulpiride	3 (2.4%)
Amiloride + Spironolactone	2 (1.6%)
Chlorpheniramine maleate + Potassium Chloride	2 (1.6%)
Ciprofloxacin + Ivabradine	1 (0.8%)
Amiodarone + Clarithromycin	1 (0.8%)
Gentamicin + Mannitol	1 (0.8%)
Pheniramine maleate + Nitroglycerin	1 (0.8%)

Supplementary Table S3

List of DDIs included in all three KBs with the same risk rating		
Drug pair	**Risk rating (Drugs.com- Lexicomp- Micromedex)**	**Frequency/125 patients (%)**
1. Amiloride ↔ potassium chloride	MAJOR- D- MAJOR	1 (0.8%)
2. Amiodarone ↔ digoxin		13 (10.4%)
3. Amiodarone ↔ warfarin		14 (11.2%)
4. Amiodarone ↔ simvastatin		1 (0.8%)
5. Aspirin ↔ warfarin		7 (5.6%)
6. Atorvastatin ↔ clarithromycin		1 (0.8%)
7. Clopidogrel ↔ omeprazole		5 (4%)
8. Clopidogrel ↔ warfarin		2 (1.6%)
9. Potassium chloride ↔ spironolactone		11 (8.8%)
10. Pyrazinamide ↔ rifampin		1 (0.8%)
11. Albuterol ↔ furosemide/ torsemide	MODERATE- C- MODERATE	18 (14.4%)
12. Albuterol ↔ hydrochlorothiazide		2 (1.6%)
13. Alprazolam ↔ diltiazem		1 (0.8%)
14. Aminophylline/ theophylline ↔ Amiodarone		3 (2.4%)
15. Amiodarone ↔ β-blockers (Atenolol/Bisoprolol/carvedilol/ propranolol)		6 (4.8%)
16. Amiodarone ↔ atorvastatin		7 (5.6%)
17. Aspirin ↔ insulin		17 (13.6%)
18. Aspirin ↔ prednisone		1 (0.8%)
19. Aspirin ↔ streptokinase		2 (1.6%)
20. Aspirin/ ibuprofen ↔ levofloxacin/ norfloxacin/ ofloxacin		14 (11.2%)
21. Aspirin/ ketorolac/ tenoxicam ↔ ramipril/ enalapril/captopril		40 (32%)
22. Bisoprolol ↔ ketorolac/ tenoxicam		2 (1.6%)
23. Bisoprolol/ propranolol ↔ Insulin		4 (3.2%)
24. Captopril/ enalapril/ lisinopril/ perindopril/ ramipril ↔ Furosemide/torsemide		39 (31.2%)
25. Carvedilol ↔ glimepiride/ glyburide		2 (1.6%)
26. Ceftriaxone ↔ warfarin		1 (0.8%)
27. Dexamethasone ↔ warfarin		2 (1.6%)
28. Digoxin ↔ bumetanide / furosemide/ torsemide		42 (33.6%)
29. Digoxin ↔ bisoprolol		2 (1.6%)
30. Glimepiride ↔ ranitidine		1 (0.8%)
31. Glimepiride ↔ warfarin		1 (0.8%)
32. Hydrochlorothiazide ↔ enalapril/ ramipril		2 (1.6%)
33. Omeprazole ↔ warfarin		4 (3.2%)
34. Ramipril ↔ tenoxicam/nimesulide		5 (4%)
35. Ranitidine ↔warfarin		4 (3.2%)
36. Rifaximin ↔warfarin		1 (0.8%)
37. Vitamin E ↔ warfarin		1 (0.8%)
38. Aspirin ↔ phenytoin	MINOR- B- MINOR	1 (0.8%)

Supplementary Table S4

Combinations and frequency of the "triple whammy" treatment regimen	N (%) N=30
ACEI/Diuretic/NSAID	
Ramipril + furosemide + spironolactone + low-dose aspirin	5 (16.1)
Ramipril + torsemide + spironolactone + low-dose aspirin	2 (6.5)
Ramipril + torsemide + low-dose aspirin	1 (3.2)
Ramipril + furosemide + spironolactone + low-dose aspirin + tenoxicam	1 (3.2)
Ramipril + furosemide + spironolactone + low-dose aspirin + nimesulide	2 (6.5)
Ramipril + torsemide + low-dose aspirin + nimesulide	1 (3.2)
Captopril + furosemide + low-dose aspirin	1 (3.2)
Captopril + furosemide + spironolactone + tenoxicam	1 (3.2)
Captopril + furosemide + spironolactone + low-dose aspirin	3 (9.7)
Captopril + torsemide + spironolactone + low-dose aspirin	1 (3.2)
Captopril + furosemide + spironolactone + low-dose aspirin + diclofenac sodium	2 (6.5)
Enalapril + furosemide + spironolactone + low-dose aspirin	1 (3.2)
Lisinopril + torsemide + spironolactone + low-dose aspirin	1 (3.2)
ARA/Diuretic/NSAID	
Valsartan + furosemide + spironolactone + low-dose aspirin	3 (9.7)
Valsartan + furosemide + hydrochlorothiazide + low-dose aspirin	1 (3.2)
Valsartan + enalapril + hydrochlorothiazide + low-dose aspirin	1 (3.2)
Candesartan + torsemide + spironolactone + low-dose aspirin	1 (3.2)
Candesartan + furosemide + spironolactone + hydrochlorothiazide + low-dose aspirin	2 (6.5)

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/26621