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RESEARCH ARTICLE

Non-cardiovascular medication and readmission for heart failure: an observational cohort study

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Abstract

Background Among heart failure (HF) patients, hospital readmissions are a major concern. The medication taken by a patient may provide information on comorbidities and conditions and may be used as an indicator to identify populations at an increased risk of HF readmission. *Aim* This study explored the use of non-cardiovascular medication at hospital discharge from the first HF admission in search of indicators of high risk of readmission for HF. *Method* The study included 22,476 HF patients from the Dutch PHARMO Database Network at their first HF hospitalization. The data was divided into training and validation sets. A Cox regression model with demographics, date of first HF hospital admission and non-cardiovascular medication present at discharge, adjusted for cardiovascular medication, was developed in the training set and subsequently implemented in the validation set. *Results* The study included 22,476 patients, mean age 76.7 years (range 18–104) and median follow-up time 2.5 years (range 0–15.7 years). During the study period 6,725 (29.9%) patients were readmitted for HF, with a median time-to-readmission of 7 months (range 0–14.3 years). Non-cardiovascular medication associated with a high risk of readmission for HF were identified as indicators of high risk, with no implied causal relationship. Patients prescribed antigout medications presented a 25% increased risk of readmission (HR 1.25, 95%CI 1.09–1.45, $P=0.002$). Patients using insulin had an 18% higher risk of readmission versus patients not using insulin (HR 1.18, 95%CI 1.06–1.32, $P=0.002$), but not versus patients treated with other blood-glucose-lowering drugs. No association between the risk of readmission and NSAIDs use was observed. *Conclusion* The results suggest that diabetes is responsible for the higher HF-readmission risk observed in patients prescribed insulin. The observed risk in users of antigout medication should be further investigated. The absence of an association with the use of NSAIDs should be interpreted with caution.

Keywords Diabetes · Epidemiology · Heart failure · Hospitalization · Medication · Readmission

Impacts on practice

- Patients prescribed insulin have an increased risk of readmission for HF. The increased risk disappeared when only patients with type 2 diabetes were studied, suggesting that the diabetes disease itself may be responsible for the observed increased risk.
- Patients prescribed antigout medication had a higher risk of readmission for HF. Therefore, intensive monitoring is warranted, irrespective of whether the observed risk is due to the medication itself or the condition as such.

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Introduction

Despite improvements in the prevention and treatment of heart failure (HF), it is still a substantial healthcare burden, particularly due to high rates of hospital readmissions [1, 2]. In Europe, the incidence of HF is about 5/1000 person-years in adults, and the prevalence 1–2% [3]. Due to population growth, ageing and the increasing prevalence of comorbidities, the absolute number of hospital admissions for HF is expected to increase considerably in the future, probably as much as 50% in the next 25 years. There are global efforts to prevent HF, as well as practice guidelines for optimal management of the disease [3–5].

At the turn of the century, four main groups of medications formed the cornerstone of HF treatment: diuretics for symptom relief, and the disease modifying drugs angiotensin-converting-enzyme inhibitors/angiotensin-receptor blockers, beta-blockers and mineralocorticoid-receptor antagonists. Only in 2016, a new treatment modality was introduced: the angiotensin receptor-neprilysin inhibitor (ARNI). In the 2016 ESC guidelines ARNI had acquired a recommendation for the treatment of HF [6]. The sodium-glucose co-transporter inhibitors, have acquired an important evidence-based position in the 2021 ESC guidelines. Vericuguat and omecamtiv mecarbil are mentioned in the same guidelines, the level of recommendation is pending.

Special attention should however be given to comorbidities, which are present in the majority of HF patients. Comorbidities associated with worse outcomes include hypertension, diabetes, obesity, hypothyroidism, chronic obstructive pulmonary disease, gout, arthritis and anaemia [3, 4, 7, 8]. The patient's clinical characteristics and the pharmacological treatment of comorbidities may affect HF therapy and the subsequent outcome [9]. Additionally, several medical treatments for comorbidities are known to be associated with higher cardiovascular risk and are discouraged in HF patients. For example, thiazolidinediones and non-steroid anti-inflammatory drugs (NSAIDs) may lead to an increased risk of HF hospitalization and are therefore not recommended in HF patients [3]. In the years 2000–2015 no innovative new medication was introduced into the market. This relatively 'motionless' period is therefore ideal for studying the role of comorbidities and comedication.

Patient characteristics, comorbidities and medication may all affect the risk for hospital readmission of HF patients. However, in the absence of a complete medical history, the set of medication taken by a patient (the medication profile) may serve as a proxy of the patient's health status and provide information on their risk of readmission.

Aim

This hypothesis-generating study aimed to identify non-cardiovascular medications that, when present at hospital discharge, may serve as indicators of a higher risk of readmission for HF, without implying a causal relationship.

Ethics approval

The study fulfilled the requirements of the PHARMO Compliance Commission. The protocol for this retrospective cohort study was exempt from requiring IRB review and the use of de-identified secondary use data from medical records in the PHARMO Database Network was exempt from requiring informed consent from the patients. We followed the Guidelines for Good Pharmacoepidemiology Practices.

Method

Study design and data source

We performed a hypothesis-generating observational cohort study in adult HF patients from the PHARMO Database Network [10], particularly from the PHARMO Hospitalisation database and the PHARMO Out-patient Pharmacy database. Data from the PHARMO Hospitalisation database, including hospital admission and discharge records (e.g. diagnosis and dates) from the national Dutch Hospital Data Foundation, was linked to the PHARMO Out-patient Pharmacy Database, which provided information on medication from primary- and secondary-care prescriptions dispensed by outpatient pharmacies, coded according to the Anatomical Therapeutic Chemical (ATC) classification System. The PHARMO Database Network represents more than 4 million inhabitants throughout the Netherlands. Its linkage algorithms have been validated, and the network forms a representative sample of the Dutch population [11].

Study population

Patients from the PHARMO Hospitalisation database with their first HF hospital admission between January 2001 and December 2015 were included in the study. HF hospital admissions were defined by a primary discharge diagnosis of HF (ICD-9 428; ICD-10 I50) or hypertensive heart disease with (congestive) HF (ICD-9 402; ICD-10 I11.0). The first admission for HF was identified when there was no known previous HF admission in at least 3 years, assuming that

patients in the Dutch healthcare system will be admitted to the same hospital with a readmission for HF. The discharge day from the first HF hospital admission was set as the study index date. Information on comorbidities in the General Practitioner Database of the PHARMO Database Network was very limited. Therefore, a successful linkage was not possible.

Variables of interest and data handling

The risk indicators of interest were sex, age at admission, date and duration of first admission and the non-cardiovascular medications at hospital discharge from the first admission. Non-cardiovascular medications were grouped by therapeutic class according to the ATC classification codes. Different ATC levels were chosen based on the heterogeneity of the groups. Similarly, when different safety profiles across agents from the same therapeutic class were expected (e.g. different generations of sulfonylureas [12]), the individual active ingredients were studied.

Medication data was collected from the dispensing records of outpatient pharmacies. Based on periods of uninterrupted data availability for both pharmacy and hospital admission data around the time of the admission, for each patient, periods of uninterrupted use were formed prior to the analysis. Only patients with drugs dispensed before as well as after admission were included, including at least one cardiovascular drug (ATC group C, cardiovascular system) at discharge. The data included cardiovascular as well as non-cardiovascular medication.

The study outcome was readmission for HF. When more than one readmission followed the first admission, the first readmission was defined as the outcome. Follow-up started on the discharge day of the first admission and continued until the earliest of the following: outcome (i.e. readmission for HF) or the end of the study period (i.e. 31 December, 2015). More details were previously reported [13].

Statistical analysis

The complete data set was divided at random into two sets: a 'training set' and a 'validation set'. The training set was used to develop the study model, and the validation set was used to assess model reproducibility. Patient characteristics in both data sets were described. In the training set, preselection of indicators among non-cardiovascular medication was conducted based on univariate analyses (chi-square and Kaplan–Meier) and clinical rationale (e.g. drugs that can prolong the QT interval). A list of pre-selected non-cardiovascular medication (potential indicators) is shown in the Supplementary Material S1, where they are indicated with an [a]. Then, multivariate Cox regression analysis was conducted including the potential indicators (i.e. age, sex, year and duration of the first admission, and the pre-selected non-cardiovascular medications), with adjustment for cardiovascular treatment and antithrombotic agents (ATC code C Cardiovascular system and B01 Antithrombotic agents). To obtain a parsimonious model, a backward stepwise method was employed, resulting in a narrower selection of non-cardiovascular medication variables, which are described in Table 1 and in the Supplementary Material S1, where they are indicated with a [b]. Subsequently, the model developed in the training set was implemented in the validation set. Bootstrapping was used for internal validation of the parsimonious Cox regression model in both data sets, and the concordance index (C-index) was calculated in both the training and the validation sets. Results from both data sets were presented as hazard ratios (HR) with 95% confidence intervals (CI), along with counts and percentages of the dichotomous variables.

Sensitivity analyses were performed to assess how modifying the follow-up time or the inclusion/exclusion criteria impacted the results. These sensitivity analyses were performed for a maximum follow-up of 3, 6, 12 and 24 months, by excluding patients < 50 years old, and by excluding patients already readmitted on the day of discharge. Additionally, the models were also run grouping the NSAIDs as a single variable (i.e. acetic acid derivatives and related substances, oxicams, propionic acid derivatives and coxibs).

Statistical analyses were performed using IBM® SPSS Statistics 25.0. A schematic description is included in the electronic Supplementary Material S2.

Post hoc analysis on diabetes patients

Following the findings on the risk of readmission for HF in patients treated with insulin, and since diabetes is a known risk factor for HF, a post hoc analysis was performed on a subgroup of type 2 diabetes (T2D) patients, defined as those treated with at least one blood-glucose-lowering drug other than insulin in the complete dataset. Due to the consequently reduced sample size, this post hoc analysis included every T2D patient from the overall data set (not distinguishing across the training and validation sets).

Results

The study included 22,476 patients with a mean age of 76.7 years (range 18–104) and a median follow-up time of 2.5 years (range 0–15.7 years). During the study period, 6725 (29.9%) patients were readmitted for HF, with a median time-to-readmission of 7 months (range 0–14.3 years). Overall, the incidence rate of readmission was about 80 per 1000 person-years. The training set included 11,180 patients, and the validation set 11,296 patients. Descriptive characteristics

Table 1 Results from the multivariate cox regression model in the training and validation set

	Training set N*	Training set HR (95%CI)	Validation set N*	Validation set HR (95%CI)
Number of patients	11,180		11,296	
Age, years, mean (SD)	76.8 (10.9)	1.01 (1.00–1.01)	76.7 (10.87)	1.01 (1.00–1.01)
Male gender (reference: female)	5460 (48.8%)	1.05 (0.98–1.13)	5567 (49.3%)	1.15 (1.07–1.23)
Year of fist admission, median (IQR)	2008 (2005–2011)	0.98 (0.97–0.99)	2008 (2005–2011)	0.98 (0.97–0.99)
Duration (days) of first admission, median (IQR)	6 (3–11)	1.00 (0.99–1.00)	6 (3–11)	1.00 (1.00–1.00)
Drugs for acid related disorders				
Proton pump inhibitors	4164 (37.2%)	1.05 (0.97–1.13)	4154 (36.8%)	1.06 (0.99–1.15)
Drugs used in diabetes				
Insulins	1160 (10.4%)	1.21 (1.09–1.35)	1088 (9.6%)	1.18 (1.06–1.32)
Sulfonylureas				
Glibenclamide	87 (0.8%)	0.84 (0.57–1.25)	98 (0.9%)	0.96 (0.67–1.38)
Tolbutamide	420 (3.8%)	1.19 (1.01–1.41)	388 (3.4%)	1.23 (1.04–1.47)
Gliclazide	321 (2.9%)	0.90 (0.73–1.12)	290 (2.6%)	1.22 (1.01–1.49)
Glimepiride	441 (3.9%)	1.14 (0.97–1.34)	431 (3.8%)	1.22 (1.04–1.43)
DPP-4 inhibitors	35 (0.3%)	1.99 (1.24–3.18)	18 (0.2%)	0.98 (0.44–2.19)
Systemic corticosteroids	947 (8.5%)	0.89 (0.77–1.01)	920 (8.1%)	0.93 (0.81–1.07)
Anti-inflammatory and antirheumatic products,non-steroids, as a group	382 (3.4%)	0.76 (0.61–0.94)	439 (3.9%)	0.73 (0.59–0.88)
Acetic acid derivatives & related substances	192 (1.7%)	0.78 (0.58–1.05)	205 (1.8%)	0.87 (0.67–1.14)
Oxicams	47 (0.4%)	0.94 (0.53–1.66)	53 (0.5%)	0.59 (0.32–1.10)
Propionic acid derivatives	81 (0.7%)	0.84 (0.55–1.30)	103 (0.9%)	0.60 (0.39–0.92)
Coxibs	67 (0.6%)	0.61 (0.35–1.08)	71 (0.6%)	0.61 (0.36–1.03)
Antigout medications	632 (5.7%)	1.30 (1.14–1.49)	544 (4.8%)	1.25 (1.09–1.45)
Antipsychotics with QT prolongation	243 (2.2%)	0.75 (0.56–1.02)	237 (2.1%)	0.80 (0.59–1.08)
Selective serotonin reuptake inhibitors	454 (4.1%)	0.79 (0.65–0.96)	443 (3.9%)	0.96 (0.79–1.15)
Drugs for obstructive airway diseases				
Adrenergics, inhalants	1492 (13.3%)	1.08 (0.97–1.22)	1552 (13.7%)	1.14 (1.02–1.27)
Anticholinergics	1361 (12.2%)	1.10 (0.98–1.24)	1249 (11.1%)	0.91 (0.81–1.02)
Theophylline	72 (0.6%)	0.69 (0.42–1.11)	91 (0.8%)	0.61 (0.38–0.97)

Proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole); Insulins (fast acting, intermediate acting, intermediate- or long acting, and long acting); DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, and combinations); Acetic acid derivatives & related substances (indometacin, sulindac, diclofenac, acenofenac); Oxicams (piroxicam, meloxicam); Propionic acid derivatives (ibuprofen, naproxen, ketoprofen, flurbiprofen, tiaprofenic acid, dexibuprofen, naproxen-esomeprazole); Coxibs (celecoxib, rofecoxib, valdecoxib, etoricoxib); Antigout preparations (allopurinol, febuxostat, benzbromarone, colchicine); Antipsychotics with QT prolongation (thioridazine, haloperidol, flupentixol, zuclopenthixol, pimozide, sulpiride); Selective serotonin reuptake inhibitors (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram); Adrenergics, inhalants (salbutamol, terbutaline, fenoterol, salmeterol, formoterol, indacaterol, olodaterol, vilanterol); Anticholinergics (ipratropium bromide, tiotropium bromide, aclidinium bromide, glycopyrronium bromide, umeclidium bromide)

HR hazard ratio of the cox regression model

N*, Number and % of patients, unless otherwise specified

of both sets are shown in Table 1. Both the training set and the validation set had similar patient characteristics, follow-up times and times to readmission.

The HRs of the selected potential indicators are shown in Table 1. Among the selected potential confounders, no impact on the model was observed for age or date and duration of first admission. Male sex, with a HR 1.15 (95%CI 1.07–1.23, $P < 0.001$) in the validation set, had not presented a statistically significant hazard in the training set ($P > 0.5$). Among the non-cardiovascular medication, insulin (prescribed to 9.6% of the patients in the validation set) presented a HR of 1.18 (95%CI. 1.06–1.32, $P = 0.003$) in the validation set, consistent with the training set. Among the sulfonylureas, while tolbutamide, gliclazide and glimepiride had significant HRs of about 1.2 in the validation set, this was only observed for tolbutamide in the training set (HR 1.19, 95%CI 1.01–1.41, $P = 0.038$). Among the NSAIDs, the propionic acid derivatives

presented a HR of 0.60 (95%CI 0.39–0.92, $P = 0.022$) in the validation set, which was not consistent with that in the training set. Conversely, when all NSAIDs were combined (sensitivity analysis), the HR was 0.73 (95%CI 0.59–0.88, $P = 0.001$) in the validation set similar to that in the training set (0.76). Antigout medication presented an increased hazard (HR 1.25, 95%CI 1.09–1.45, $P = 0.002$) in the validation set, consistent with the training set. Proton pump inhibitors, systematic corticosteroids, antipsychotics with known QT prolongation and drugs for obstructive airway disease did not contribute significantly to the model. Selective serotonin reuptake inhibitors indicated protection in the training set, but this effect was neither confirmed in the validation set nor in the sensitivity analyses. In conclusion, among the selected potential indicators, only some of the medication used in diabetes treatment, some NSAIDs and antigout medication presented a statistically significant ($P < 0.05$) HR in the training set as well as in the validation set.

The sensitivity analyses with follow-up periods of 6, 12 and 24 months supported the observed HR > 1 for gout medication but was less robust with regard to the observed findings for insulin (Supplementary material S5). The HR for NSAIDs were not influenced by different follow-up times. Analyses excluding patients < 50 years old and excluding patients readmitted on the day of discharge show similar results. Additional information on the results of bootstrapping, Harrell's C statistics and sensitivity analyses are included in the Supplementary Material S6.

The post hoc analysis in T2D included 4300 T2D patients as a subgroup. No significant associations with the risk of readmission were found by Kaplan–Meier analysis for insulin, metformin, sulfonylureas, thiazolidinediones and dipeptidyl peptidase 4 inhibitors. This result was confirmed by Cox regression analysis.

Discussion

Statement of key findings

This observational cohort study aimed to provide new insights regarding non-cardiovascular medication use as a potential indicator of the risk of readmission of HF patients. The use of insulin was associated with a higher risk of readmission versus non-insulin-treated HF patients, but not versus HF patients with T2D treated with other blood-glucose-lowering drugs. The study results supported previous assumptions such as that of an increased cardiac risk associated with patients prescribed antigout medication. No association between the risk of readmission and NSAIDs was observed.

Strengths and weaknesses

The key strengths of the study are the large number of medications studied, as well as the use of observational data from a large group of HF patients, reflecting the real-world setting in the Netherlands. Thus, it is expected that the results of this study will be applicable to HF patients in the Dutch population. Additionally, the consistency observed between the training and the validation sets supports the robustness of the study results.

A limitation of this study is the lack of clinical information regarding comorbidities, and thus the risk of confounding by indication. However, the identified medication associated with a high risk of readmission for HF is treated as an indicator and no causal inference should be applied. An additional limitation is the assumption that the medication in the profile at hospital discharge may aid in the prediction of a high risk of readmission independently of the follow-up time. In order to investigate this assumption, sensitivity analyses were performed, modifying the follow-up time. These analyses supported the observed HR > 1 for gout medication but were less robust with regard to the observed findings for insulin. The HR for NSAIDs were not influenced by variations in the follow-up times.

The low bias achieved in bootstrap analyses showed the statistical robustness of the model, although the low Harrell's C value obtained, defining the ability of the model to predict the outcome, was poor. Since the study was performed only on patients with HF, and physicians prescribe medications by applying their knowledge on contraindications and preferable treatment based on the patient's profile, it is assumed that the results may reflect fewer high-risk medication in patients with a high risk of readmission, a paradox that will influence the C-index directly.

Interpretation

Drugs used in diabetes

Diabetes is a risk factor in HF, and poor glycaemic control and albuminuria are both associated with an increased risk of HF [14, 15]. In this study, one fourth of the study patients were prescribed diabetes treatment, and insulin prescription was associated with an increase of 18% in the risk of readmission. While the observed association may be explained by the presence of diabetes alone, one may also consider that insulin induces sodium retention [3, 16], which may contribute to exacerbated fluid retention, resulting in worse cardiac outcomes. Additionally, a study in T2D patients with HF suggested that insulin was associated with worse outcomes of HF, compared to non-insulin diabetes treatment [17]. However, our findings in the subgroup of T2D patients showed no increased risk of readmission in patients

with insulin when compared to patients treated with blood-glucose-lowering drugs, other than insulin. Thus, our post hoc analysis in the T2D population suggests that the risk observed in our main analysis may be a consequence of the lack of adjustment for the comorbidity diabetes. It could also be that the presence of diabetes itself is more important than the severity of it, as insulin is not used as first-line treatment in T2D [18–20].

The results for blood-glucose-lowering drugs, other than insulin are diverse. Metformin, a first-line medication for T2D generally associated with cardiovascular benefits [15, 21–23], was not associated with readmissions for HF. There are cardiovascular safety concerns over the use of sulfonylureas [12]. Thiazolidinediones are contraindicated in HF patients [3, 15, 16] due to side-effects and were rarely prescribed to the study patients.

For now, further research into existing medications is limited as new glucose-lowering drugs such as sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide-1 analogues in patients with heart failure are being positioned [24].

NSAIDs

An interesting finding of this study is the beneficial trend observed in patients prescribed NSAIDs, which is not in accordance with the issued warning on the use of NSAIDs, that they cause fluid retention, increase the risk of myocardial infarction and are associated with various other cardiovascular adverse events [25, 26].

The availability and reimbursement of NSAIDs in the Netherlands throughout the years has changed. Short-term use for conditions such as headache will not be reimbursed by health insurance, and the drug must be obtained over the counter. The majority of NSAID use may therefore not have been captured because NSAIDs are available both by prescription and over the counter. In general, higher doses for more continuous use will be recorded in the PHARMO database. This concerns, for example, NSAIDs prescribed by a rheumatologist for severe rheumatoid arthritis. Cardiologists will advise against the use of NSAIDs by HF patients, but when these are prescribed by other medical specialists, e.g. rheumatologists or orthopaedic surgeons, the use of an NSAID will be accepted and might lead to intensified monitoring of the patient, resulting in a decreased risk of readmission for HF. Therefore, this particular finding should be interpreted with caution.

Antigout medications

The $\geq 25\%$ increased risk of readmission observed in patients prescribed antigout medications may well be due to the underlying abnormal levels of uric acid in the blood. Gout, mainly characterized by constantly elevated levels of uric acid in the blood, is associated with a higher risk of HF and a worse outcome [27, 28]. Additionally, elevated uric acid is common in HF patients and it is a well-known side effect of diuretics, especially thiazides, a common treatment in symptomatic HF patients [3]. Patients suffering more severe HF, who have an increased risk of readmission, do use more diuretics and are therefore more likely to be prescribed antigout medications. Furthermore, coexisting impaired renal function may increase the incidence of gout [29]. Therefore, this result probably does not reflect the risk associated with the medication itself but with the condition the medication is intended to treat. Nevertheless, the high statistical significance and robustness of the results across the main and sensitivity analyses underlines the need to be aware of this risk and suggests further investigation.

Implications for practice and further research

In further research, it should be confirmed that the increased risk observed in T2D patients is caused by the comorbidity itself and not by insulin. The beneficial trend observed in patients prescribed NSAIDs should be interpreted with caution. Patients either with gout or prescribed antigout medication should be observed more closely.

Conclusion

This hypothesis-generating study explored non-cardiovascular comedication in search of indicators identifying patients with an increased risk of HF readmission after the first HF admission, without implying a causal relationship between the identified medication and the associated risk. HF patients prescribed insulin presented a higher risk of readmission versus other HF patients, but no additional risk against T2D HF patients treated with other blood-glucose-lowering drugs was observed. This finding suggests that diabetes may be a risk factor in readmission for HF. Prescription of antigout medications at discharge after HF hospitalization was associated with an increase in the risk of readmission. The absence of an association with the use of NSAIDs should be interpreted with caution.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-022-01418-3.

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Conflicts of interest Parallel to this research at Medisch Spectrum Twente (MST), Enschede, the Netherlands, the author Enriqueta Vallejo-Yagüe worked at Synovo GmbH (Tübingen, Germany, pharmaceutical biotech company engaged in discovery and drug development). Conflicts of interest for the other authors: none declared.

References

1. Desai AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? Circulation. 2012;126(4):501–6. https://doi.org/10.1161/circulationaha.112.125435.
2. Jhund PS. The recurring problem of heart failure hospitalisations. Eur J Heart Fail. 2020;22(2):249–50. https://doi.org/10.1002/ejhf.1721.
3. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726. https://doi.org/10.1093/eurheartj/ehab368.
4. Atherton JJ, Sindone A, Pasquale CGD, et al. National heart foundation of Australia and cardiac society of Australia and New Zealand: guidelines for the prevention, detection, and management of heart failure in Australia 2018. Heart Lung Circ. 2018;27:1123–208. https://doi.org/10.1016/j.hlc.2018.06.1042.
5. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. Circulation. 2017;136:e137–61. https://doi.org/10.1161/cir.0000000000000509.
6. Ponikowski P, Voors AA, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the european society of cardiology (ESC). developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J. 2016;37:2129–200. https://doi.org/10.1093/eurheartj/ehw128.
7. van Deursen VM, Urso R, Laroche C, et al. Co-morbidities in patients with heart failure: an analysis of the European heart failure pilot survey. Eur J Heart Fail. 2014;16(1):103–11. https://doi.org/10.1002/ejhf.30.
8. Triposkiadis F, Giamouzis G, Parissis J, et al. Reframing the association and significance of co-morbidities in heart failure. Eur J Heart Fail. 2016;18:744–58. https://doi.org/10.1002/ejhf.600.
9. Page RL, O'Bryant CL, Cheng D, et al. Drugs that may cause or exacerbate heart failure: a scientific statement from the American heart association. Circulation. 2016;134(6):e32-69. https://doi.org/10.1161/cir.0000000000000426.
10. PHARMO Database Network: What we have. https://pharmo.nl/what-we-have/pharmo-database-network/. Accessed 31 Oct 2021
11. Van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven cancer registry and the PHARMO record linkage system. Eur J Cancer. 2010;46:395–404. https://doi.org/10.1016/j.ejca.2009.09.010.
12. Kumar R, Kerins DM, Walther T. Cardiovascular safety of antidiabetic drugs. Eur Heart J Cardiovasc Pharmacother. 2016;2:32–43. https://doi.org/10.1093/ehjcvp/pvv035.
13. Kruik-Kollöffel WJ, Linssen GCM, Kruik HJ, et al. Effects of European society of cardiology guidelines on medication profiles after hospitalisation for heart failure in 22,476 Dutch patients: from 2001 till 2015. Heart Fail Rev. 2019;24:499–510. https://doi.org/10.1007/s10741-019-09777-2.
14. Rosengren A, Vestberg D, Svensson A-M, et al. Long-term excess risk of heart failure in people with type 1 diabetes: a prospective case-control study. Lancet Diabetes Endocrinol. 2015;3:876–85. https://doi.org/10.1016/S2213-8587(15)00292-2.
15. Seferović PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the heart failure association of the European society of cardiology. Eur J Heart Fail. 2018;20(5):853–72. https://doi.org/10.1002/ejhf.1170.
16. Gilbert RE, Krum H. Heart failure in diabetes: effects of antihyperglycaemic drug therapy. Lancet. 2015;385:2107–17. https://doi.org/10.1016/S0140-6736(14)61402-1.
17. Cosmi F, Shen L, Magnoli M, et al. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. Eur J Heart Fail. 2018;20:888–95. https://doi.org/10.1002/ejhf.1146.
18. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323. https://doi.org/10.1093/eurheartj/ehz486.
19. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. Last updated Dec 2020, 16. Available from https://www.nice.org.uk/guidance/ng28/chapter/Recommendations#drug-treatment-2. Accessed 31 Oct 2021
20. Barents ESE, Bilo HJG, Bouma M, et al. Diabetes mellitus type 2. NHG, Dutch College of General Practitioners. September 2018. https://richtlijnen.nhg.org/standaarden/diabetes-mellitus-type-2. Accessed 31 Oct 2021
21. Azimova K, Juan ZS, Mukherjee D. Cardiovascular safety profile of currently available diabetic drugs. Ochsner J. 2014;14:616–32.
22. Yandrapalli S, Jolly G, Horblitt A, et al. Cardiovascular benefits and safety of non-insulin medications used in the treatment of type 2 diabetes mellitus. Postgrad Med. 2017;129:811–21. https://doi.org/10.1080/00325481.2017.1358064.
23. Hippisley-Cox J, Coupland C. Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: cohort study in primary care. BMJ. 2016;354:i3477. https://doi.org/10.1136/bmj.i3477.
24. Seferović PM, Coats AJS, Ponikowski P, et al. European society of cardiology/heart failure association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. Eur J Heart Fail. 2020;22(2):196–213. https://doi.org/10.1002/ejhf.1673.
25. Fanelli A, Ghisi D, Aprile PL, et al. Cardiovascular and cerebrovascular risk with nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors: latest evidence and clinical implications. Ther Adv Drug Saf. 2017;8:173–82.
26. Schmidt M, Lamberts M, Schjerning Olsen A, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for cardiovascular pharmacotherapy of the European society of cardiology. Eur Heart J. 2016;37(13):1015–23. https://doi.org/10.1093/eurheartj/ehv505.
27. Huang H, Huang B, Li Y, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail. 2014;16:15–24. https://doi.org/10.1093/eurjhf/hft132.
28. Tedeschi A, Agostoni P, Pezzuto B, et al. Role of comorbidities in heart failure prognosis part 2: chronic kidney disease, elevated serum uric acid. Eur J Prev Cardiol. 2020;27(2_Suppl):35–45. https://doi.org/10.1177/2047487320957793.
29. Dalbeth N, Merriman TR, Stamp LK. Gout Lancet. 2016;388(10055):2039–2052. https://doi.org/10.1016/S0140-6736(16)00346-9