ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 1499–1511
doi:10.1002/ejhf.2271

RESEARCH ARTICLE

Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden)

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Received 13 May 2021; revised 8 June 2021; accepted 12 June 2021; online publish-ahead-of-print 28 June 2021

Aims Use and dosing of guideline-directed medical therapy (GDMT) in patients with heart failure (HF) have been shown to be suboptimal. Among new users of GDMT in HF, we followed the real-life patterns of dose titration and discontinuation of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, mineralocorticoid receptor antagonists (MRA) and angiotensin receptor–neprilysin inhibitors (ARNI).

Methods and results New users were identified in health care databases in Sweden, UK and US between 2016–2019. Inclusion criterion was a recent HF hospitalization (HHF) triggering the initiation of GDMT. Patients were grouped by GDMT, i.e. ACEi, ARB, beta-blocker, MRA and ARNI, and stratified by initial dose. Follow-up was 12 months, until death or study end. Outcomes were dose titration within each drug class, discontinuation and first HHF or death. Dose/discontinuation follow-up was assessed daily based on the coverage length of a filled prescription and reported on day 365. New users of ACEi (n = 8426), ARB (n = 2303), beta-blockers (n = 10 476), MRA (n = 17 421), and ARNI (n = 29 546) were identified. Over 12 months, target dose achievement was 15%, 10%, 12%, 30%, and discontinuation was 55%, 33%, 24% and 27% for ACEi, ARB, beta-blockers and ARNI, respectively. MRA was rarely titrated and discontinuation rates were high (40%). Event rates for HHF or death ranged from 40.0–86.9 per 100 patient-years across the treatment groups.

Conclusion Despite high risk of clinical events following HHF, new initiation of GDMT was followed by consistent patterns of low up-titration and early GDMT discontinuation in three countries with different health care and economies. Our data highlight the urgent need for moving away from long sequential approach when initiating HF treatment and for improving just-in-time decision support for patients and health care providers.

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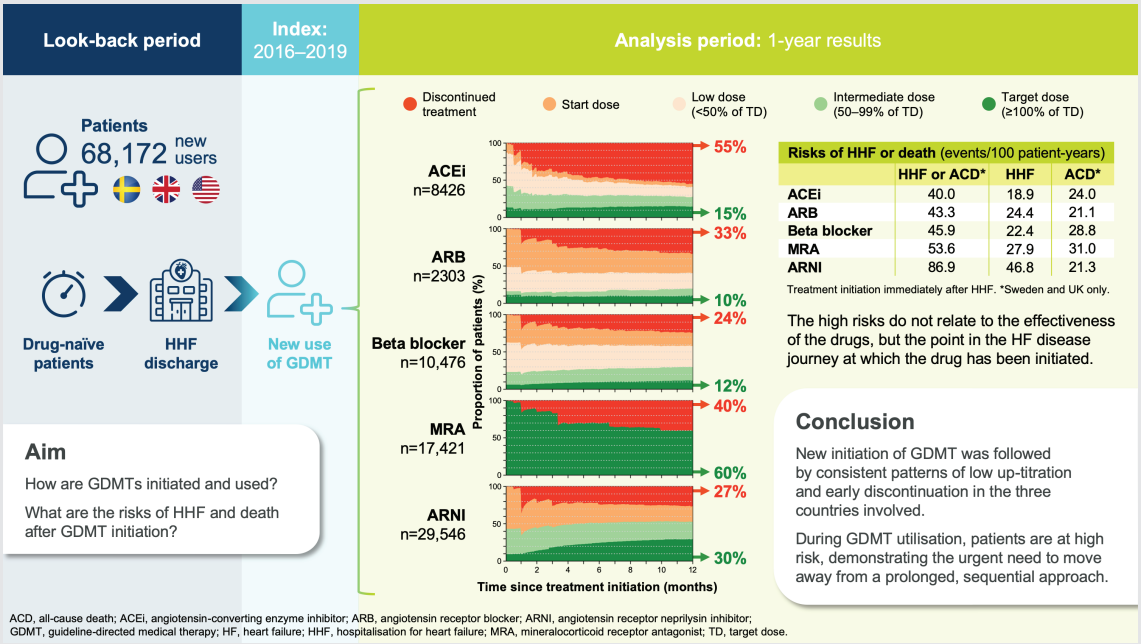
Graphical Abstract



New users were identified in health care databases in Sweden, UK and US between 2016–2019. Inclusion criterion was a recent HHF triggering the initiation of GDMT. Patients were grouped by GDMT, i.e. ACEi, ARB, beta-blocker, MRA and ARNI, and stratified by initial dose. Follow-up was 12 months, until death or end of the registry. Outcomes were dose titration within each drug class, discontinuation and first HHF or all-cause death. Dose/discontinuation follow-up was assessed daily based on the coverage length of a filled prescription and reported on day 365. Due to the different structure of the registries used for the current analysis, the time-windows adopted for identifying previous use of the drug differed across the three countries. In particular, in UK and Sweden the filled prescriptions for the treatments were checked since 2013 and 2014, respectively, i.e. wash-out of 3 and 2 years, respectively, whereas in the US it was limited to 6 months. The 1-year longer wash-out in UK vs. Sweden was due to the fact that UK patients living in rural areas often receive prescriptions once/twice yearly covering the entire year rather than monthly, and therefore a longer wash-out period was deemed necessary. Even shorter wash-out in the US was due to the frequent changes in healthcare insurance providers, which would have led to a limited number of patients with data available 2 or 3 years prior to HHF. Furthermore, recent HHF was defined as 7 days prior to the initiation of GDMT in Sweden and US, but prior to 30 days in UK where patients are typically provided with 1-month drug supply at discharge.

Keywords Heart failure with reduced ejection fraction • Guideline-directed medical therapy • Angiotensin-converting enzyme inhibitor • Angiotensin receptor blocker • Beta-blocker • Mineralocorticoid receptor antagonist • Angiotensin receptor–neprilysin inhibitor

Introduction

Guideline-directed medical therapy (GDMT) in heart failure with reduced ejection fraction (HFrEF) consists of several pharmacological classes which need up-titration to target dose in order to achieve the prognostic and clinical effects shown in large randomized clinical trials (RCTs).[1–8] Accordingly, current international heart failure (HF) guidelines recommend initiation at a low dose (start dose) followed by up-titration to target (or the highest tolerable dose) under close medical surveillance to monitor for kidney function, potassium levels, hypotensive episodes, bradycardia, and other potential side effects.[9,10] More specifically, the European Society of Cardiology (ESC) guidelines recommend sequential initiation of the different classes, starting with a renin–angiotensin system inhibitor (RASi) and a beta-blocker, followed by a mineralocorticoid receptor antagonist (MRA), and then sacubitril/valsartan in replacement of RASi. Sodium–glucose co-transporter 2 inhibitors (SGLT2i) have recently been approved by regulatory agencies for the treatment of HFrEF. They carry beneficial effects on mortality/morbidity and quality of life, with no need for titration (single dose administration) and fewer safety concerns compared with traditional HFrEF medications.[11–14] The ESC guidelines on HF

will be soon updated to include SGLT2i in their therapeutic algorithm for HFrEF.[15–17] An Expert Consensus Decision Pathway document from the American College of Cardiology currently recommends to initiate treatment with angiotensin receptor–neprilysin inhibitor (ARNI) or RASi, with the former preferred, together with a beta-blocker, and then to add MRA or SGLT2i.[18]

Previous reports have shown undertreatment and underdosing of GDMT in patients with HFrEF.[19–23] However, to our knowledge, limited data exist regarding the initiation of HF drugs and patterns of longitudinal up-titration or discontinuation among patients with newly diagnosed HFrEF in a real-world clinical setting.

Therefore, using health care data from three countries we assessed doses at initiation, patterns of dose titration or discontinuation for each of the most commonly prescribed HFrEF drug within each pharmacological class when newly initiated after a hospitalization for HF (HHF), as well as 1-year risk of HHF and all-cause death.

Methods

In this observational cohort study, new users of established HFrEF drugs were identified in large and representative electronic health records in Sweden (nationwide registries), United Kingdom (CPRD Aurum) and United States (IBM MarketScan®, Commercial and Medicare Supplemental databases), see online supplementary material for detailed descriptions. HHF was defined according to the International Statistical Classification of Diseases and Related Health Problems (ICD) version 9 and 10 codes 428.0, 428.9, 402.9 and I50, I11.0, I13.0, I13.2, respectively. HF diagnosis has been validated in all these three administrative registries with high validity, i.e. 95% in Sweden, 87% in the UK and 84% in the US.[24–26] Data on left ventricular ejection fraction (EF) and laboratory measurements were not available in these data sources.

Study population

New users of the most frequently used drug within each investigated pharmacological class, i.e. angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, MRA and ARNI, in each country between 2016–2019 were included (online supplementary *Table S1*). Therefore, in Sweden, UK and US, respectively, enalapril, ramipril and lisinopril were considered as representative of the ACEi class; candesartan, candesartan and losartan as ARBs; metoprolol, bisoprolol and carvedilol as beta-blockers; and spironolactone and sacubitril/valsartan as MRA and ARNI, respectively, regardless of country.

A new initiation of GDMT was defined as the day of first ever filled prescription for these drugs. To be considered for inclusion, the date of initiation had to occur during 2016–2019, without any previous filled prescription for any drug from the same pharmacological class (*Graphical Abstract*). Furthermore, to ensure that the prescribed indication for the use of these treatments was HF and not e.g. hypertension, a recent HHF prior to new use was required. Due to the different structure of the registries used for the current analysis, the time-windows adopted for identifying previous use of the drug differed across the three countries. In particular, in UK and Sweden the filled prescriptions for the treatments were checked since 2013 and 2014, respectively, i.e. wash-out of 3 and 2 years, respectively, whereas in the US it was limited to 6 months. The 1-year longer wash-out in UK vs. Sweden was due to the fact that UK patients living in rural areas often receive prescriptions once/twice yearly covering the entire year rather than monthly, and therefore a longer wash-out period was deemed necessary. Even shorter wash-out in the US was due to the frequent changes in healthcare insurance providers, which would have led to a limited number of patients with data available 2 or 3 years prior to HHF. Furthermore, recent HHF was defined as 7 days prior to the initiation of GDMT in Sweden and US, but prior to 30 days in UK where patients are typically provided with 1-month drug supply at discharge. New users of ARNI were not required to have a recent HHF since the indication is restricted to HF and previous RASi use was allowed for the titration analyses. The five GDMT drug classes were analysed independently, and thus a patient might have been included in more than one cohort.

Baseline characteristics

Patient characteristics were described at the index date, and included demographics, comorbidities and treatments. Comorbidities were defined by an ICD code in any position at or prior to the index date, whereas use of drugs was defined whether at least one dispensation was identified during the year prior to the index date. Detailed definitions of the variables are provided in online supplementary *Tables S2* and *S3*.

Follow-up and outcomes

New users were followed up up to 12 months, with censoring at death, loss to follow-up or at the end of registry follow-up. Drug dosing was categorized as follows: start dose (recommended initiation dose), low dose (receiving <50% of target dose), intermediate dose (50–99% of target dose), target dose (≥100% of target dose), and discontinued. Discontinuation was defined by the lack of a new filled prescription following a previous one. Drugs were assumed to be taken according to the guideline recommendations, i.e. enalapril and ramipril twice daily (BID) and the other treatments once daily (OD). The duration of each filled prescription was calculated based on the number of days covered by the number of pills contained in the box and the prescribed dose.[27,28] If a new dispensation was registered before the previous one had ended, the new treatment period started immediately if there was a change in dose (thus considered as a switch in dose), otherwise it started at the end of the previous one. When the pills collected through a dispensation were over, a patient was considered as off treatment until a new package was collected. The percentages of target dose and discontinuations were calculated each day as number of observations within each dose or number of discontinuations, respectively, divided by the total number of patients in the analyses on that day. Patients who died or were lost to follow-up prior to day 365 were then removed from the denominator used for the calculations. In the case of a switch, e.g. from RASi to sacubitril/valsartan, the treatment was considered discontinued after that the time frame covered by the filled prescription was over.

Outcomes were time to first HHF, defined as a hospital admission with HF as primary diagnosis, or all-cause death (i.e. composite outcome), as well as HHF and all-cause death separately. Mortality data were not available in the US cohort. Patients who did not experience the outcome were censored whether lost to follow-up or at day 365 (online supplementary *Table S4*).

Statistical analysis

Statistical analyses were performed within each country/registry and then aggregated data were pooled for overall descriptions. All

analyses were primarily descriptive, with no formal comparison across countries. Baseline characteristics are summarized as means (standard deviations) for continuous variables and frequencies (percentages) for categorical variables. Starting and low/intermediate/target doses were defined according to current guidelines, as reported in online supplementary *Table S5*.

Drug titration patterns are derived for each day over the 1-year follow-up/until end of follow-up and presented as percentages. Event rates for outcomes were calculated as number of events per 100 patient-years. For event-rate estimations, in the ARNI group an immediate HHF discharge prior to new initiation was required similarly to the other treatment groups.

Analyses on drug titration over time were repeated based on age strata (<70 vs. ≥70 years), gender, and presence of chronic kidney disease (CKD). Drug titration and discontinuation analyses were repeated with the assumption of OD use for ACEi whereas BID dose is recommended, i.e. for enalapril in Sweden and for ramipril in UK.

Results

Baseline characteristics

Overall, 68 172 new users of HF drugs were identified, with 8426 receiving an ACEi, 2303 an ARB, 10 476 a beta-blocker, 17 421 an MRA and 29 546 ARNI (*Table 1*). Across all countries, patients who initiated ACEi, ARB and beta-blockers had lower rates of ischaemic heart disease and diabetes compared with the new users of MRA and ARNI. New users of ARNI were generally younger, less likely

Table 1 Baseline characteristics of heart failure patients initiated on heart failure medical therapies in Sweden, UK and US (pooled data)

	ACEi	ARB	Beta-blocker	MRA	ARNI	HHF ARNI[a]
Patients, *n*	8426	2303	10 476	17 421	29 546	1868
Index year, *n* (%)						
2016	3053 (36)	667 (29)	3440 (33)	5327 (31)	4319 (15)	181 (10)
2017	2662 (32)	620 (27)	3236 (31)	4953 (28)	7019 (24)	500 (27)
2018	2010 (24)	681 (30)	2694 (26)	4448 (26)	8350 (28)	655 (35)
2019	701 (8)	335 (15)	1106 (10)	2693 (15)	9858 (33)	532 (28)
Age, years, mean (SD)	70 (15)	71 (15)	70 (15)	75 (13)	65 (13)	67 (13)
Female sex, *n* (%)	3688 (44)	1071 (47)	4302 (41)	7908 (45)	8075 (27)	474 (25)
Duration of last HHF, days, mean (SD)	8 (8)	7 (7)	9 (10)	9 (8)	6 (8)	7 (6)
Ischaemic heart disease, *n* (%)	3863 (46)	1073 (47)	4699 (45)	9367 (54)	20 756 (70)	1277 (68)
Myocardial infarction	1831 (22)	534 (23)	2203 (21)	5298 (30)	12 951 (44)	839 (45)
Unstable angina	554 (7)	227 (10)	724 (7)	2727 (16)	5411 (18)	516 (28)
Coronary revascularization	1129 (13)	204 (9)	1569 (15)	2915 (17)	5891 (20)	384 (21)
Angina pectoris	2954 (35)	855 (37)	3435 (33)	7107 (41)	18 182 (62)	1054 (56)
Stroke, *n* (%)	1215 (14)	416 (18)	1484 (14)	3189 (18)	2442 (8)	323 (17)
Atrial fibrillation/flutter, *n* (%)	3627 (43)	997 (43)	3990 (38)	10 102 (58)	13 064 (44)	947 (51)
Peripheral artery disease, *n* (%)	1033 (12)	349 (15)	1282 (12)	2362 (14)	4811 (16)	299 (16)
CKD, *n* (%)	2438 (29)	743 (32)	3879 (37)	5609 (32)	9511 (32)	703 (38)
Diabetes, *n* (%)	2262 (27)	741 (32)	3480 (33)	5917 (34)	12 379 (42)	790 (42)
Cancer, *n* (%)	2043 (24)	583 (25)	2392 (23)	4980 (29)	6522 (22)	421 (23)
HF drug treatment, *n* (%)	3282 (39)	1129 (49)	4106 (39)	13 736 (79)	28 056 (95)	1691 (91)
RASi	0 (0)	0 (0)	3861 (37)	10 928 (63)	23 047 (78)	1405 (75)
ACEi	0 (0)	0 (0)	2449 (23)	6872 (39)	14 828 (50)	869 (47)
ARB	0 (0)	0 (0)	1531 (15)	4655 (27)	9613 (33)	632 (34)
Beta-blocker	3125 (37)	1082 (47)	0 (0)	11 318 (65)	26 535 (90)	1552 (83)
MRA	468 (6)	182 (8)	575 (5)	0 (0)	15 320 (52)	972 (52)
Sacubitril/valsartan	362 (4)	9 (0)	133 (1)	14 (0)	0 (0)	0 (0)
SGLT2i	53 (1)	79 (3)	92 (1)	161 (1)	1003 (3)	64 (3)
Other HF treatments, *n* (%)	3167 (38)	935 (41)	3626 (35)	11 043 (63)	21 000 (71)	1489 (80)
Loop diuretics	2012 (24)	519 (23)	2472 (24)	8580 (49)	8871 (30)	1005 (54)
Digoxin	382 (5)	125 (5)	326 (3)	1583 (9)	3596 (12)	243 (13)
Device therapy[a]	416 (9)	102 (9)	601 (10)	1830 (14)	4308 (39)	452 (39)
Nitrates, *n* (%)	700 (8)	253 (11)	666 (6)	3043 (17)	5759 (19)	454 (24)
Warfarin, *n* (%)	858 (10)	219 (10)	711 (7)	3507 (20)	4895 (17)	387 (21)
$P2Y_{12}$ receptor antagonists, *n* (%)	490 (6)	174 (8)	615 (6)	1815 (10)	5580 (19)	308 (16)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor–neprilysin inhibitor (sacubitril/valsartan); CKD, chronic kidney disease; HF, heart failure; HHF, hospitalization for heart failure; MRA, mineralocorticoid receptor antagonist (spironolactone); RASi, renin–angiotensin system inhibitor; SD, standard deviation; SGLT2i, sodium–glucose co-transporter 2 inhibitor.
[a]Immediate HHF prior to ARNI initiation.

women, more likely to receive other HFrEF medical and device therapies compared with new users of the other investigated HF drugs. Only a small proportion of patients ($n = 1868$, 6.3%), were initiated on ARNI immediately after an HHF discharge but these patients showed similar characteristics to the overall group of new users of ARNI, except for more concomitant use of beta-blockers and loop diuretics.

Table 2 shows the baseline characteristics of the 23 407, 12 431 and 32 334 new users of HF medications identified in Sweden, UK and US, respectively. Overall, patients from the Swedish cohort were the oldest and least likely to have ischaemic heart disease, diabetes and CKD, whereas those from US were the youngest, had the highest burden of ischaemic heart disease, peripheral arterial disease and diabetes.

Initiation, titration and discontinuation

Angiotensin-converting enzyme inhibitors, ARBs and beta-blockers were generally initiated at starting or low doses (*Figure 1*). MRA was usually initiated at target dose, i.e. 25 mg, with 50 mg only rarely used. ARNI was initiated generally at higher doses compared with ACEi and beta-blockers.

Low degrees of dose titration and high discontinuation rates over 12 months were common regardless of pharmacological class and country (*Figure 1*).

Within 1 year after initiation of therapy, pooled target doses were registered in 15%, 10%, 12% and 30%, whereas pooled discontinuation rates, i.e. the proportion of patients off treatment on day 365, were 55%, 33%, 24% and 27% for ACEi, ARB, beta-blockers and ARNI, respectively (*Figure 2*). Only a minority of patients initiated on ACEi and ARB subsequentially started ARNI, i.e. 5.7% and 6.6% respectively, similar across all countries.

The majority of patients initiated with a start or low dose of ACEi, ARB and beta-blocker, remained on the same dose or discontinued within 12 months, i.e. 68%, 80% and 71%, respectively. MRA dose was titrated to 50 mg only in <5% of patients and discontinuation was frequent (i.e. 40%). When considering patients who received ARNI after a recent HHF (the HHF ARNI group, *Table 1*), similar titration and discontinuation patterns were seen compared with the analyses where all new users were included, regardless of a recent HHF (online supplementary *Figure S1*).

One-year prognosis

In total, 8549 events were observed for the combined outcome of HHF or all-cause death (*Table 3*). Event rates for HHF or all-cause death were lower in patients receiving ACEi or ARB vs. beta-blockers vs. MRA vs. ARNI (i.e. 40.0, 43.3, 45.9, 53.6 and 86.9 per 100 patient-years, respectively). Similar patterns were observed for HHF ($n = 6985$ events) but not for all-cause death, where event rates were lower in the ARNI group compared with the other groups (165 vs. events 919–3077 events). Detailed event rates per country are described in online supplementary *Table S6*.

Subgroup and sensitivity analyses

Titration was poorer in patients aged ≥70 years for ACEi, ARB and beta-blockers, whereas no relevant age-based difference was observed for ARNI (online supplementary *Figure S2*). Discontinuation rates were slightly lower for ACEi (54% vs. 56%), and higher for ARB (36% vs. 31%) and beta-blockers (26% vs. 22%) in the younger group compared with the older group. Compared with men, women showed slightly less favourable discontinuation/target dose patterns for ACEi (56%/11% vs. 54%/17%), beta-blockers (24%/9% vs. 24%/13%), MRA (41%/59% vs. 40%/60%) and ARNI (29%/25% vs. 26%/31%) (online supplementary *Figure S3*). Patients with CKD showed higher discontinuation rates for all the investigated treatments compared with those without CKD (63% vs. 52% for ACEi, 50% vs. 27% for ARB, 31% vs. 21% for beta-blockers, 51% vs. 36% for MRA, and 32% vs. 24% for ARNI) (online supplementary *Figure S4*). Target dose achievement was similar for ARB and beta-blockers, and lower for ACEi (12% vs. 19%) and ARNI (22% vs. 33%) in patients with vs. without CKD. Lower discontinuation and target dose achievement were observed when analyses were performed with an OD assumption compared with the guideline-recommended BID assumption for enalapril (Sweden) and ramipril (UK) (online supplementary *Figure S5*).

Discussion

In this observational study of 68 172 new users of HF GDMT drugs across three countries in North America and Europe, we showed that dose at the initiation of therapy is aligned with guideline recommendations but that target dose achievement is limited (10–30%), and that drug discontinuation is common (24–55%) over 1 year from initiation of therapy. Suboptimal GDMT dosing was more likely in older patients and those with CKD. Importantly, patients were at high risk of HHF and death while optimization of HF medical therapy was ongoing.

Limited titration to target dose of guideline-directed medical therapies

The prognostic benefit linked with optimization of HF medications has been highlighted previously in clinical trials and observational studies.[22,29–33] In an analysis of the BIOSTAT-CHF (The Biology Study to Tailored Treatment in Chronic Heart Failure) population, patients who did not reach >50% of target dose with RASi or beta-blockers reported an increased risk of HHF or death compared with those who reached the target dose.[22] However, despite this prognostic advantage, there are data highlighting underuse and underdosing of GDMT in daily clinical practice. In CHAMP-HF (Change the Management of Patients with Heart Failure) enrolling 2588 US patients with chronic HFrEF and no contraindications to medical therapy, over a period of 12 months RASi was started/up-titrated in 7%, beta-blockers in 10% and ARNI in 10% of the population.[21] Target doses of HF medications were achieved only in a minority of patients (8.5%, 18.4% and 1.5%, respectively). Also, underuse was common with a large proportion of patients with an indication not receiving treatments

Table 2 Baseline characteristics of heart failure patients initiated on heart failure medical therapies in Sweden, UK and US

	Sweden (n = 23 407)					UK (n = 12 431)					US (n = 32 334)				
	Enalapril	Candesartan	Metoprolol	MRA	ARNI	Ramipril	Candesartan	Bisoprolol	MRA	ARNI	Lisinopril	Losartan	Carvedilol	MRA	ARNI
Patients, n	2521	1044	2806	9172	7864	2084	104	3480	3548	3214	3821	1155	4189	4701	18 468
Index year, n (%)															
2016	842 (33)	215 (21)	783 (28)	2443 (27)	465 (6)	630 (30)	35 (34)	1023 (29)	1119 (32)	288 (9)	1581 (41)	417 (36)	1634 (39)	1765 (38)	3566 (19)
2017	686 (27)	239 (23)	760 (27)	2355 (26)	1477 (19)	653 (31)	21 (20)	1049 (30)	1032 (29)	939 (29)	1323 (35)	360 (31)	1427 (34)	1566 (33)	4603 (25)
2018	528 (21)	282 (27)	616 (22)	2142 (23)	2458 (31)	578 (28)	31 (30)	966 (28)	969 (27)	1346 (42)	904 (24)	368 (32)	1112 (27)	1337 (28)	4546 (25)
2019	465 (18)	308 (30)	647 (23)	2232 (24)	3464 (44)	223 (11)	17 (16)	443 (13)	428 (12)	641 (20)	13 (0)	10 (1)	16 (0)	33 (1)	5753 (31)
Age, years, mean (SD)	76 (14)	75 (14)	74 (14)	79 (11)	69 (12)	74 (15)	76 (13)	76 (14)	77 (12)	67 (12)	65 (16)	66 (16)	62 (16)	65 (15)	62 (13)
Female sex, n (%)	1140 (45)	485 (46)	1097 (39)	4399 (48)	1714 (22)	927 (44)	55 (53)	1569 (45)	1623 (46)	781 (24)	1621 (42)	531 (46)	1636 (39)	1886 (40)	5580 (30)
Duration of last HHF, days, mean (SD)	7 (5)	7 (5)	7 (6)	8 (6)	6 (5)	11 (12)	13 (18)	12 (14)	14 (14)	7 (8)	6 (7)	6 (7)	7 (8)	7 (7)	7 (8)
Coronary ischaemic disease, n (%)	678 (27)	324 (31)	700 (25)	4168 (45)	4700 (60)	1029 (49)	59 (57)	1712 (49)	2141 (60)	2360 (73)	2156 (56)	690 (60)	2287 (55)	3058 (65)	13 696 (74)
Myocardial infarction	370 (15)	176 (17)	386 (14)	2715 (30)	3511 (45)	478 (23)	40 (38)	824 (24)	1126 (32)	1495 (47)	983 (26)	318 (28)	993 (24)	1457 (31)	7945 (43)
Unstable angina	222 (9)	113 (11)	253 (9)	1970 (21)	3069 (39)	122 (6)	15 (14)	243 (7)	389 (11)	434 (14)	210 (5)	99 (9)	228 (5)	368 (8)	1908 (10)
Coronary revascularization	125 (5)	62 (6)	113 (4)	939 (10)	1127 (14)	733 (35)	40 (38)	1148 (33)	1501 (42)	1827 (57)	271 (7)	102 (9)	308 (7)	475 (10)	2937 (16)
Angina pectoris	409 (16)	190 (18)	358 (13)	2781 (30)	3554 (45)	625 (30)	41 (39)	1088 (31)	1522 (43)	1593 (50)	1920 (50)	624 (54)	1989 (47)	2804 (60)	13 035 (71)
Stroke, n (%)	260 (10)	133 (13)	268 (10)	1424 (16)	928 (12)	328 (16)	22 (21)	638 (18)	791 (22)	520 (16)	627 (16)	261 (23)	578 (14)	974 (21)	994 (5)
Atrial fibrillation/flutter, n (%)	1170 (46)	486 (47)	1192 (42)	5782 (63)	4251 (54)	1102 (53)	61 (59)	1868 (54)	2328 (66)	1510 (47)	1355 (35)	450 (39)	930 (22)	1992 (42)	7303 (40)
Peripheral artery disease, n (%)	131 (5)	52 (5)	147 (5)	756 (8)	590 (8)	178 (9)	12 (12)	390 (11)	467 (13)	300 (9)	724 (19)	285 (25)	745 (18)	1139 (24)	3921 (21)
CKD, n (%)	212 (8)	119 (11)	306 (11)	1471 (16)	1378 (18)	753 (36)	49 (47)	1685 (48)	1946 (55)	1178 (37)	1473 (39)	575 (50)	1888 (45)	2192 (47)	6955 (38)
Diabetes, n (%)	289 (11)	130 (12)	456 (16)	2335 (25)	2335 (30)	474 (23)	38 (37)	1116 (32)	1226 (35)	1103 (34)	1499 (39)	573 (50)	1908 (46)	2356 (50)	8941 (48)
Cancer, n (%)	696 (28)	281 (27)	669 (24)	2876 (31)	1747 (22)	536 (26)	24 (23)	928 (27)	995 (28)	576 (18)	811 (21)	278 (24)	795 (19)	1109 (24)	4199 (23)
HF drug treatment, n (%)	1031 (41)	454 (43)	1027 (37)	7710 (84)	7678 (98)	751 (36)	48 (46)	1741 (50)	2743 (77)	3145 (98)	1500 (39)	627 (54)	1338 (32)	3283 (70)	17 233 (93)
RASi	0 (0)	0 (0)	987 (35)	6347 (69)	7462 (95)	0 (0)	0 (0)	1641 (47)	2262 (64)	3073 (96)	0 (0)	0 (0)	1233 (29)	2319 (49)	12 512 (68)
ACEi	0 (0)	0 (0)	536 (19)	3727 (41)	4468 (57)	0 (0)	0 (0)	1146 (33)	1663 (47)	2344 (73)	0 (0)	0 (0)	767 (18)	1482 (32)	8016 (43)
ARB	0 (0)	0 (0)	487 (17)	3010 (33)	3618 (46)	0 (0)	0 (0)	543 (16)	711 (20)	907 (28)	0 (0)	0 (0)	501 (12)	934 (20)	5088 (28)
Beta-blocker	1002 (40)	438 (42)	0 (0)	6592 (72)	7383 (94)	696 (33)	44 (42)	0 (0)	2010 (57)	2930 (91)	1427 (37)	600 (52)	0 (0)	2716 (58)	16 222 (88)
MRA	106 (4)	78 (7)	109 (4)	0 (0)	5967 (76)	0 (0)	15 (14)	297 (9)	0 (0)	2415 (75)	19 (0)	89 (8)	169 (4)	0 (0)	6938 (38)
Sacubitril/valsartan	0 (0)	0 (0)	20 (1)	0 (0)	0 (0)	141 (7)	0 (0)	7 (0)	14 (0)	0 (0)	221 (6)	9 (1)	17 (0)	76 (2)	0 (0)
SGLT2i	10 (0)	3 (0)	20 (1)	69 (1)	300 (4)	7 (0)	61 (59)	24 (1)	19 (1)	60 (2)	36 (1)	15 (1)	48 (1)	73 (2)	643 (3)
Other HF treatments, n (%)	872 (35)	386 (37)	764 (27)	5968 (65)	6480 (82)	983 (47)	56 (54)	1736 (50)	2604 (73)	2724 (85)	1312 (34)	493 (43)	1126 (27)	2471 (53)	11 796 (64)
Loop diuretics	738 (29)	325 (31)	626 (22)	5435 (59)	5493 (70)	854 (41)	11 (11)	1532 (44)	2431 (69)	2417 (75)	420 (11)	183 (16)	314 (7)	714 (15)	961 (5)
Digoxin	110 (4)	54 (5)	32 (1)	883 (10)	1012 (13)	116 (6)	14 (13)	220 (6)	450 (13)	540 (17)	156 (4)	57 (5)	74 (2)	250 (5)	2044 (11)
Device therapy[a]	181 (7)	83 (8)	208 (7)	1228 (13)	3168 (40)	235 (11)	19 (18)	393 (11)	602 (17)	1140 (35)	N/A	N/A	N/A	N/A	N/A
Nitrates, n (%)	250 (10)	127 (12)	186 (7)	1951 (21)	2111 (27)	205 (10)	17 (16)	319 (9)	643 (18)	931 (29)	245 (6)	109 (9)	161 (4)	449 (10)	2717 (15)
Warfarin, n (%)	330 (13)	115 (11)	185 (7)	2229 (24)	2140 (27)	242 (12)	17 (16)	378 (11)	787 (22)	767 (24)	286 (7)	87 (8)	148 (4)	491 (10)	1988 (11)
$P2Y_{12}$ receptor antagonists, n (%)	93 (4)	49 (5)	96 (3)	813 (9)	1154 (15)	151 (7)	12 (12)	335 (10)	461 (13)	632 (20)	246 (6)	113 (10)	184 (4)	541 (12)	3794 (21)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor–neprilysin inhibitor (sacubitril/valsartan); CKD, chronic kidney disease; HF, heart failure; HHF, hospitalization for heart failure; MRA, mineralocorticoid receptor antagonist (spironolactone); N/A, not available; RASi, renin–angiotensin system inhibitor; SD, standard deviation; SGLT2i, sodium–glucose co-transporter 2 inhibitor; UK, United Kingdom; US, United States.

[a]Immediate HHF prior to ARNI initiation.

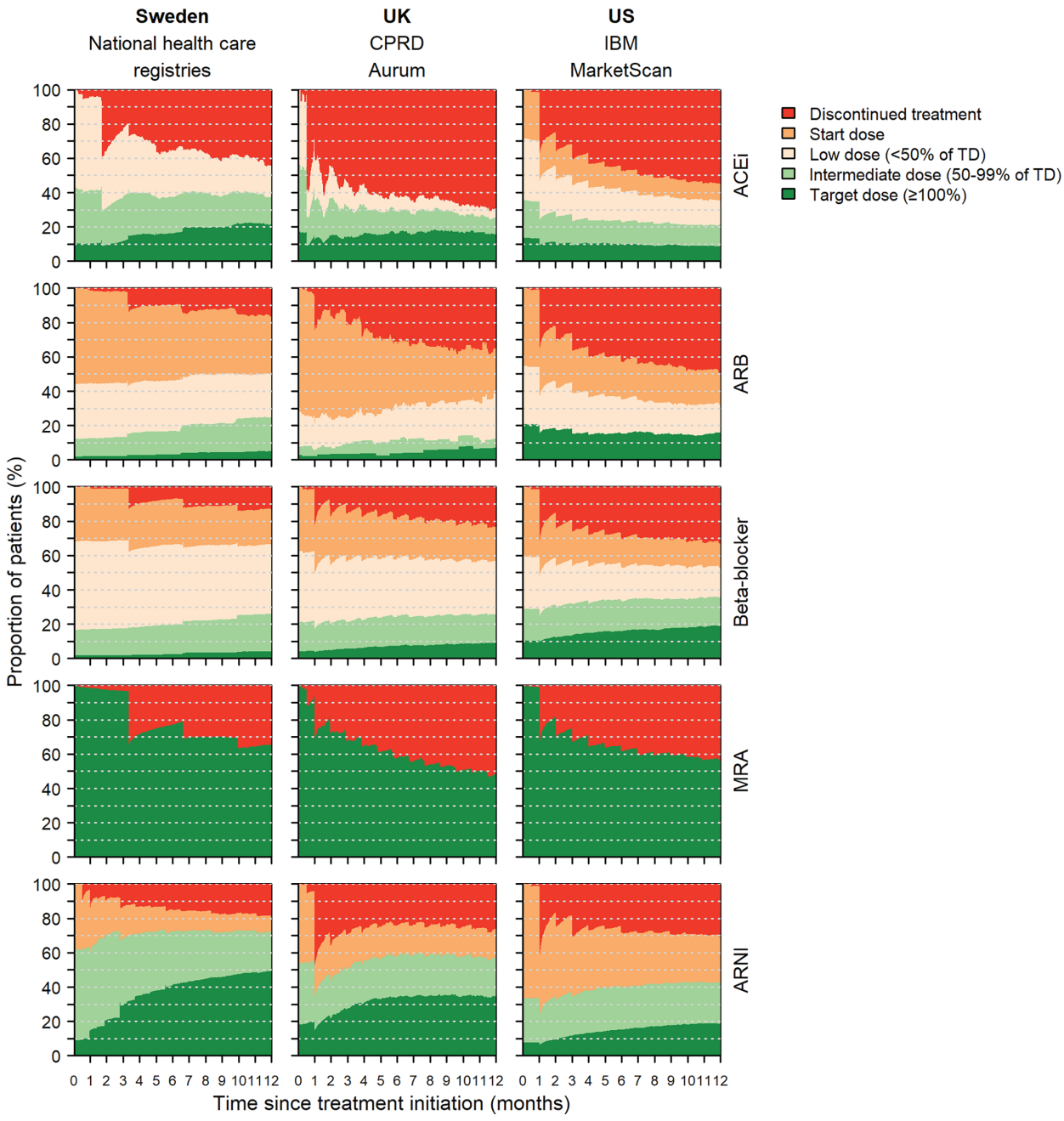


Figure 1 Titration to target dose (TD) and discontinuation of the most frequently used guideline-directed medical therapies for heart failure within each pharmacological class. In Sweden, UK and US, respectively, enalapril, ramipril, lisinopril, were representative of angiotensin-converting enzyme inhibitors (ACEi); candesartan, candesartan and losartan of angiotensin receptor blockers (ARB); metoprolol succinate, bisoprolol and carvedilol of beta-blockers. For mineralocorticoid receptor antagonists (MRA) and angiotensin receptor–neprilysin inhibitor (ARNI), spironolactone and sacubitril/valsartan, respectively, were the most used in all countries. Percentages describe dose distribution within 12 months of the index date, i.e. first dispensation.

at baseline (34%, 20%, 66% and 86% for RASi, beta-blockers, MRA and ARNI, respectively). In the population with chronic HFrEF enrolled in the ESC HF Long-Term (ESC-HF-LT) Registry, 93% of patients were treated with a RASi, 93% with a beta-blocker, and 67% with an MRA. Notably, target dose was achieved in less than 30% of patients, and almost two-thirds of them reported a reason for not achieving the target dose.[34] However, both CHAMP-HF and ESC-HF-LT registries analysed prevalent use and dose of treatments, whereas we investigated the titration process and discontinuations.

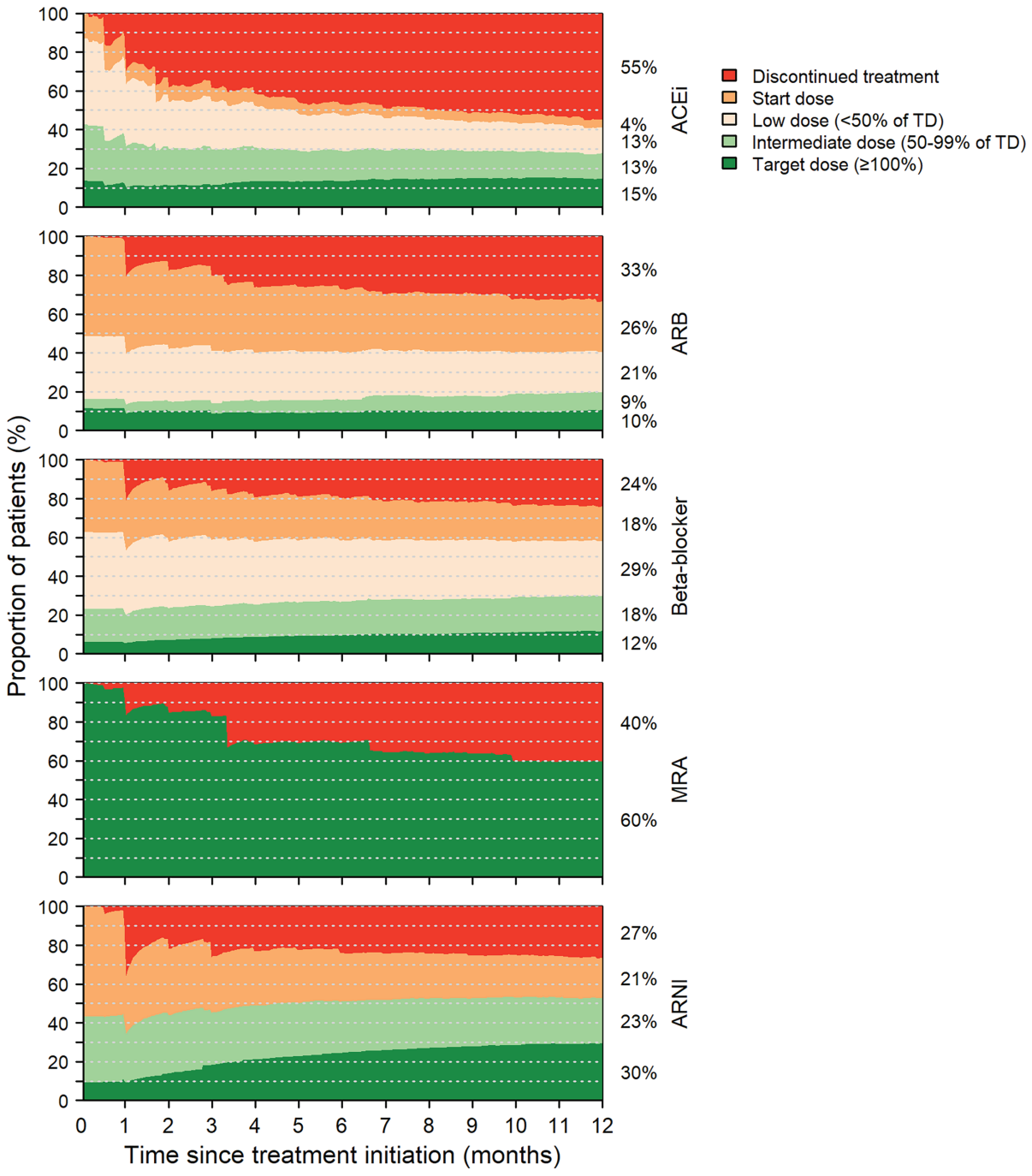


Figure 2 Pooled titration to target dose (TD) and discontinuation of the most frequently used guideline-directed medical therapies for heart failure within each pharmacological class. In Sweden, UK and US, respectively, enalapril, ramipril, lisinopril, were representative of angiotensin-converting enzyme inhibitors (ACEi); candesartan, candesartan and losartan of angiotensin receptor blockers (ARB); metoprolol succinate, bisoprolol and carvedilol of beta-blockers. For mineralocorticoid receptor antagonists (MRA) and angiotensin receptor–neprilysin inhibitor (ARNI), spironolactone and sacubitril/valsartan, respectively, were the most used in all countries.

In almost 70 000 new users of HFrEF medications across three countries, we observed that target doses were reached only in 10–18% of patients for RASi, 12% for beta-blockers, and 30% for ARNI. New ARNI users achieved the highest proportion of target dose compared with the other GDMTs. The main reason for this finding might be that most patients were on RASi prior to ARNI initiation (78%), leading to consider eligible for sacubitril/valsartan patients with less tolerability issues for starting treatment and

Table 3 Event rates for outcomes during 12-month follow-up in new users of heart failure drugs immediately after a hospitalization for heart failure discharge in Sweden, UK and US

	HHF or ACD[a]	HHF	ACD[a]
ACEi, *n* (ER per 100 patient-years)	1315 (40.0)	1154 (18.9)	919 (24.0)
ARB, *n* (ER per 100 patient-years)	334 (43.3)	386 (24.4)	188 (21.1)
Beta-blocker, *n* (ER per 100 patient-years)	1933 (45.9)	1628 (22.4)	1450 (28.8)
MRA, *n* (ER per 100 patient-years)	4484 (53.6)	3304 (27.9)	3077 (31.0)
ARNI, *n* (ER per 100 patient-years)	483 (86.9)	513 (46.8)	165 (21.3)

ACD, all-cause death; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor (sacubitril/valsartan); ER, event rate; HHF, hospitalization for heart failure; MRA, mineralocorticoid receptor antagonist (spironolactone).
[a]ACD was available in Sweden and UK.

undergoing up-titration. Consistently, patients were younger when initiated ARNI vs. other treatments, and therefore likely to have higher tolerability and better compliance to treatment and regular follow-up.[35] In our Swedish data, there were signs indicating stricter follow-up in patients receiving ARNI. Indeed, although we observed 3-month step patterns (following the normal 3-month prescription iteration) in discontinuation/up-titration of RASi, beta-blockers and MRA, for ARNI this pattern was rather monthly, indicating a closer follow-up.

The new use of an HF medication following a HHF might suggest high probability of hospitalization due to *de novo* HF, with *de novo* HF having being previously shown to represent the cause of almost half of all HFrEF hospitalizations.[36] Our analysis of incident rather than prevalent use of medication might have better allowed to capture the efforts for dose optimization which might be more intense after initiation of new therapies, but also might have fostered the identification of discontinuations which might be more frequent in new users of drugs. Additionally, evidence exists supporting better implementation of HF treatment use in registries, e.g. CHAMP-HF and ESC-HF-LT, vs. administrative health databases, i.e. our data sources, and therefore our analysis might be more representative of real-world care.[37]

Target dose achievement can be affected by a number of factors, such as tolerability and the risk of side effects,[34] which might justify underdosing and underuse to some extent, but unlikely to the degree shown in our and previous analyses.[21] Titration to the highest tolerable dose is often the most feasible approach in a real-world clinical setting where patients are older and frailer in comparison with RCTs where treatment effect is investigated and demonstrated using recommended target doses.[1–8] The perception of clinical stability, together with the organizational efforts and coordination required for rapid but safe titration process (e.g. follow-up in nurse-led HF clinics, or a stricter follow-up) might also be often obstacles to the optimization of medical therapy in patients with HFrEF.[38]

Previous studies have shown older age and the presence of CKD as major factors for HFrEF medication underuse,[39] which has also been explained by the under-representation of these patients in RCTs.[40] However, in observational analyses from the Swedish HF Registry, although octogenarians with HFrEF were less likely to receive RASi and beta-blockers, these treatments were associated with better prognosis in this age strata compared with the younger HFrEF population.[41,42] Similarly, although RASi were less used in patients with vs. without severe CKD [estimated glomerular filtration rate (eGFR) <30 vs. ≥30 mL/min/1.73 m^2: 34% vs. 84%], this treatment was associated with longer survival regardless of renal function.[43] Impaired renal function has been identified as a major reason for non-use of MRA in the same registry[43]; however, even if this was justified for severe CKD where MRA are contraindicated, it was not in patients with eGFR 30–60 mL/min/1.73 m^2 who have been shown to benefit from this treatment in RCTs.[44–46] Underdosing and underuse of HFrEF GDMT might share the same determinants. Indeed, in our analysis marked underdosing was observed in older patients and those with CKD, as also supported by other studies.[40] A perception of less benefit, competing risk due to concomitant non-HF diseases, and increased risk of adverse events with HFrEF GMDT in these categories of patients which are frequently encountered in daily clinical practice, might therefore explain underuse as well as underdosing. While costs and underinsurance remain important barriers to access and treatment persistence, the remarkable consistency of our findings across three different health economies and the extension of these treatment patterns even to established, generic therapies, suggest broader issues lending to limited treatment optimization.

Need for simplified guidelines

Underdosing or slow up-titration of GDMT might have several implications. Whether optimal doses of RASi and beta-blockers might be needed to consider treatment with ARNI and SGLT2i, this might lead to a strong delay or even prevent the use of these life-saving medications. The increased risk of HHF and all-cause death in the post-HHF phase shown in our and previous analyses,[47] together with our results highlighting higher event rates in patients receiving ACEi vs. beta-blockers vs. MRA vs. ARNI reflecting sequential GDMT initiation based on HF disease progression, highlight the need for improved and more time-sensitive treatment optimization.[48,49] These findings have important implications for clinical practice, particularly in primary care, where many patients might not receive life-saving treatments due to the limited resources and time needed for the currently used sequential approach. Our data highlights the urgent need for simplified guidelines and more rapid GDMT sequencing, but also the need for HF drugs that are well-tolerated, safe and without need for titration in order to ensure compliance to prescribed therapy.[48,49]

Frequent discontinuation of guideline-directed medical therapies

We observed a high discontinuation rate for GDMT, up to 48% for RASi. As for limited dose titration, discontinuation might be

linked with adverse events and low tolerability. Hyperkalaemia is not uncommon and often followed by RASi/ARNI and MRA interruption in patients with HFrEF.[50,51] In a previous study enrolling patients who experienced a mild hyperkalaemic event (K^+ 5.0–5.5 mmol/L), MRA was discontinued in 43% and RASi in 22%,[51] although discontinuation/dose reduction is recommended for $K^+ > 5.5$ mmol/L.[9,52] When discontinued, most patients (76%) were not reintroduced to MRA during the year following the hyperkalaemic event.[51] CKD is also often claimed as a reason for GDMT discontinuation although stopping RASi in patients with advanced CKD, for example, has been associated with overall higher mortality, higher risk of cardiovascular events and further worsening of renal function.[53]

Dedicated follow-up in specialty care or multidisciplinary HF clinics might facilitate use, titration, treatment persistence and up-titration of HFrEF medications but also discourage discontinuation due to the fear of potential late detection of adverse events (e.g. hyperkalaemia) in a setting where (i) specific characteristics (e.g. older age, CKD, multicomorbidity, low blood pressure) are less seen as an obstacle to a safe implementation of HF therapies; (ii) a stricter clinical and laboratory testing follow-up might be more easily achievable; and (iii) knowledge and experience on strategies to prevent and treat potential adverse effects are available (e.g. use of potassium binders for preventing hyperkalaemia leading to discontinuation of GDMT).[54–57]

Strengths and limitations

A strength of our study is represented by the consistency of results across three countries with different health care infrastructure and economics, i.e. public- (Sweden and UK) and insurance-based health care (US). Unlike other studies, the unique new use design allowed us to better follow up-titration and eventual discontinuation over time while describing the parallel risk of morbidity/mortality. We used a traditional adherence/persistence approach, but with the added complexity of working with treatments requiring titration to target dose. Consistent variable definitions and methods were used in all our three well-established data sources.

One main limitation of our study was the unavailability of ejection fraction assessments, and therefore we could not define whether we enrolled patients with HFrEF rather than with mid-range or preserved ejection fraction. However, the enrolment of new users of HFrEF GDMT following a HHF has been used to minimize the proportion of patients without indication. It was not possible to assess if patients were newly prescribed with HF drugs at hospital discharge or early post-discharge, e.g. outpatient follow-up visit. This might have an impact on adherence/persistence, since continuity of care and decision-making may be more concordant if outpatient clinician ordered. Our study design did not allow to determine multiple medication changes since each drug was considered in isolation. Therefore, patients with long-standing sub-optimally treated HF, e.g. with a MRA and a beta-blocker but without an ACEi, who are initiated only later on ACEi following an HF hospitalization, might be wrongly considered as with *de novo* HF in the ACEi analyses. Doses during follow-up might have been overestimated if a dose change was performed by dividing the pill. On the other hand, if the dosing was changed from OD to BID with the same dose as previous filled prescription the dose is underestimated. New use of a GDMT in the present analysis does not strictly reflect in which sequential order the drugs were initiated, since long-standing HF with sub-optimal treatment, e.g. MRA and beta-blocker treatment prior to RASi initiation, could be present. Patients who were switched from ACEi and ARBs to ARNI, around 6% of patients for each class, were considered as discontinuing RASi, which led to overestimate discontinuation rates for these treatments. The different registries used in this analysis have different design and characteristics. Consecutively, different definitions of recent HHF and wash-out period were adopted based on the specific registry. However, despite these differences, results were consistent across the countries. No data on vital signs and laboratory measurements (e.g. renal function, potassium levels, blood pressure) to assess reasons for initiation, discontinuation or dose changes, were available, and therefore we cannot discriminate whether these were explained by tolerability issues or poor patient compliance rather than physician's decision. However, we performed subgroup analyses to separately investigate older patients and those with CKD, who are more likely to have contraindications, report adverse events and have multiple comorbidities. No mortality data were available in the US cohort. For enalapril and ramipril, BID dosing (guideline-recommended) was assumed since the actual dosing was not available. When applying the BID assumption for enalapril and ramipril, we observed titration and discontinuation spikes followed by rapid recovery (online supplementary *Figure S5*). This might highlight that our BID assumption may not be fully representative in a clinical setting and that OD use was probably used to a significant extent. Hence, this might indicate drug mismanagement and that the results from our primary analysis might have overestimated discontinuation and underestimated target dose achievements to some extent for these drugs. MRA doses <25 mg were not available and hence were counted as 25 mg.

Conclusions

In Sweden, UK and US, despite the high risk of HHF and death, underdosing/slow up-titration and early discontinuation of GDMT were frequent in patients hospitalized for HF who were naïve to HF therapies. Our data highlight the urgent need for simplified guidelines and tools facilitating decision-making to support a rapid sequencing and prevent inappropriate discontinuation of, and increase compliance to, GDMT in HF patients. The removal of organizational barriers and the establishment of financial incentives might contribute to optimize HF management and facilitate an on-time access to appropriate treatments.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

We are grateful to Joanna Huang, Jil Billy Mamza and Susanna Jerström at AstraZeneca for logistic support and valuable comments on the manuscript. Rachel Zhang and Matt Arnold are acknowledged for statistical work with UK and US data, respectively.

Funding

This work was sponsored by AstraZeneca.

Conflict of interest: G.S. reports grants and personal fees from Vifor, AstraZeneca, grants and non-financial support from Boehringer Ingelheim, personal fees from Società Prodotti Antibiotici, Roche, Servier, GENESIS, Medtronic, and Cytokinetics, grants from MSD, Novartis, Boston Scientific, outside the submitted work. J.B. holds a full-time position at AstraZeneca as an epidemiologist. A.N. has received honoraria from MSD, AstraZeneca, Eli Lilly, Boehringer Ingelheim and Novo Nordisk. P.S. is an employee and shareholder of AstraZeneca. M.T. is employed by an independent statistical consultant company, Statisticon AB, Uppsala, Sweden, of which AstraZeneca Nordic-Baltic is a client. M.R.C. received grants from Medtronic, Boston Scientific, Abbott, Bayer and ResMed during the conduct of the study and has served as a consultant/advisor/steering committee member for Novartis, Servier, Bayer, Boston Scientific, Abbott, ResMed, NovoNordisk, Neurotronik, and FIRE1Foundry. He is a consultant to AstraZeneca as their Chief Physician Scientist (Heart Failure). G.C.F. consults for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Edwards, Janssen, Medtronic, Merck, and Novartis. M.V. has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, and Relypsa, speaker engagements with Novartis and Roche Diagnostics, and participates on clinical endpoint committees for studies sponsored by Galmed and Novartis. A.J.S.C. reports personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Gore, Impulse Dynamics and Respicardia, outside the submitted work.

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