

Appendix Table 1. Full table of patient characteristics including all comorbidity and co-medication use.

<i>Demographics/characteristics</i>	THIN			Mondriaan		
	All Cases	Discordant Cases	Concordant Cases	All Cases	Discordant Cases	Concordant Cases
	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>
<i>Patients*</i>	9,682	2,905	6,777	277	92	168
<i>Age</i>						
Mean	77.6	77.6	77.7	79.2	81.4	78.1
Std. Dev.	13.4	13.3	13.5	14.6	11.7	15.8
<i>Sex</i>						
Female	7,608 (78.6)	2,247 (77.3)	5,361 (79.1)	217 (78.3)	70 (76.1)	131 (78.0)
Male	2,074 (21.4)	658 (22.7)	1,416 (20.9)	60 (21.7)	22 (23.9)	37 (22.0)
<i>Co-morbidity</i>						
Average Number per Patient	1.20	1.38	1.12	0.98	1.22	0.95
<i>Co-medication</i>						
Average Number per Patient	1.72	2.02	1.59	2.40	2.72	2.48
<i>Observation period</i>						
Mean (years)	6.6	6.3	6.7	5.5	5.0	5.9
Median (years)	7.4	6.8	7.7	5.9	4.9	6.2
<i>Treatment episode</i>						
Mean (days)	323	202	401	458	332	582
Median (days)	87	70	112	221	191	283
<i>Prescriptions</i>						
Average Number per Patient	29.34	22.89	32.11	31.23	20.90	38.01
Co-morbidity						
Previous fracture	2,360 (24.4)	753 (25.9)	1,607 (23.7)	78 (30.0)	29 (31.5)	49 (29.2)
Rheumatoid arthritis (not including osteoarthritis)	279 (2.9)	97 (3.3)	182 (2.7)	-	-	-
Osteoporosis	1,211 (12.5)	406 (14.0)	805 (11.9)	25 (9.6)	11 (12.0)	14 (8.3)

Paget's disease	29 (0.3)	12 (0.4)	17 (0.3)	-	-	-
Anaemia	1,150 (11.9)	401 (13.8)	749 (11.1)	36 (13.8)	13 (14.1)	23 (13.7)
Epilepsy / seizures	248 (2.6)	76 (2.6)	172 (2.5)	3 (1.2)	1 (1.1)	2 (1.2)
Syncope	527 (5.4)	195 (6.7)	332 (4.9)	16 (6.2)	7 (7.6)	9 (5.4)
Ischaemic heart disease	1,272 (13.1)	442 (15.2)	830 (12.2)	21 (8.1)	10 (10.9)	11 (6.5)
Cerebrovascular disease	1,117 (11.5)	386 (13.3)	731 (10.8)	18 (6.9)	9 (9.8)	9 (5.4)
Malignant neoplasms	1,404 (14.5)	504 (17.3)	900 (13.3)	22 (8.5)	8 (8.7)	14 (8.3)
Inflammatory bowel disease	97 (1.0)	38 (1.3)	59 (0.9)	1 (0.4)	-	1 (0.6)
Obstructive airway disease	999 (10.3)	354 (12.2)	645 (9.5)	18 (6.9)	9 (9.8)	9 (5.4)
Liver disease	84 (0.9)	27 (0.9)	57 (0.8)	-	-	-
Chronic renal failure	125 (1.3)	49 (1.7)	76 (1.1)	-	-	-
Mental disorders	201 (2.1)	82 (2.8)	119 (1.8)	17 (6.5)	6 (6.5)	11 (6.5)
Dementia and/or Alzheimer	493 (5.1)	192 (6.6)	301 (4.4)	16 (6.2)	9 (9.8)	7 (4.2)
Co-medication						
Glucocorticoids (systemic)	468 (4.8)	184 (6.3)	284 (4.2)	21 (8.1)	9 (9.8)	12 (7.1)
Inhaled glucocorticoids	325 (3.4)	110 (3.8)	215 (3.2)	8 (3.1)	1 (1.1)	7 (4.2)
Bisphosphonate use	502 (5.2)	178 (6.1)	324 (4.8)	19 (7.3)	5 (5.4)	14 (8.3)
Raloxifene	15 (0.2)	4 (0.1)	11 (0.2)	-	-	-
Strontium ranelate	17 (0.2)	5 (0.2)	12 (0.2)	-	-	-
Parathyroid hormone	-	-	-	-	-	-
Calcium & vitamin D	32 (0.3)	15 (0.5)	17 (0.3)	17 (6.5)	5 (5.4)	12 (7.1)
Calcitonin	2 (0.0)	2 (0.1)	-	-	-	-
Antidepressants (neither TCAs - N06AA nor SSRIs - N06AB)	242 (2.5)	99 (3.4)	143 (2.1)	11 (4.2)	3 (3.3)	8 (4.8)

Antipsychotics/lithium	490 (5.1)	214 (7.4)	276 (4.1)	24 (9.2)	5 (5.4)	19 (11.3)
Anti-Parkinson drugs	218 (2.3)	76 (2.6)	142 (2.1)	6 (2.3)	2 (2.2)	4 (2.4)
Anticonvulsants	369 (3.8)	143 (4.9)	226 (3.3)	19 (7.3)	9 (9.8)	10 (6.0)
Bronchodilators	850 (8.8)	287 (9.9)	563 (8.3)	28 (10.8)	7 (7.6)	21 (12.5)
Antihypertensive drugs	2,705 (27.9)	909 (31.3)	1,796 (26.5)	-	-	-
Diuretics	2,174 (22.5)	689 (23.7)	1,485 (21.9)	71 (27.3)	34 (37.0)	37 (22.0)
Anti-arrhythmics	108 (1.1)	40 (1.4)	68 (1.0)	3 (1.2)	3 (3.3)	-
Sedating antihistamines	29 (0.3)	15 (0.5)	14 (0.2)	-	-	-
Estrogen-containing hormone replacement therapy (HRT)	94 (1.0)	35 (1.2)	59 (0.9)	8 (3.1)	1 (1.1)	7 (4.2)
Thyroid hormones	601 (6.2)	174 (6.0)	427 (6.3)	14 (5.4)	6 (6.5)	8 (4.8)
Antithyroid drugs	26 (0.3)	7 (0.2)	19 (0.3)	-	-	-
Disease-modifying anti-rheumatic drug (DMARD)	132 (1.4)	43 (1.5)	89 (1.3)	4 (1.5)	1 (1.1)	3 (1.8)
Thiazolidinediones	52 (0.5)	11 (0.4)	41 (0.6)	2 (0.8)	-	2 (1.2)
Antidiabetics	522 (5.4)	156 (5.4)	366 (5.4)	39 (15.0)	14 (15.2)	25 (14.9)
Antiemetic (Metoclopramide)	195 (2.0)	92 (3.2)	103 (1.5)	13 (5.0)	8 (8.7)	5 (3.0)
Anticoagulants	309 (3.2)	99 (3.4)	210 (3.1)	89 (34.2)	36 (39.1)	53 (31.5)
Morphine/opiate	1,118 (11.5)	435 (15.0)	683 (10.1)	42 (16.2)	20 (21.7)	22 (13.1)
Two or more prescriptions for a non-steroidal anti-inflammatory drug (NSAIDs)	851 (8.8)	297 (10.2)	554 (8.2)	19 (7.3)	5 (5.4)	14 (8.3)
Statins	1,309 (13.5)	448 (15.4)	861 (12.7)	32 (12.3)	10 (10.9)	22 (13.1)
Proton pump inhibitors	1,679 (17.3)	613 (21.1)	1,066 (15.7)	74 (28.5)	27 (29.3)	47 (28.0)
Aromatase Inhibitors	52 (0.5)	19 (0.7)	33 (0.5)	2 (0.8)	2 (2.2)	-
Benzodiazepines	1,153 (11.9)	460 (15.8)	693 (10.2)	101 (38.8)	37 (40.2)	64 (38.1)

* Number of patients eligible and included in the SCCS. For CCO patients without enough follow-up time before the HF for at least one control moment were excluded (350 patients in THIN and 17 in Mondriaan).

Appendix Table 2. Sensitivity analysis of the CCO design in THIN & Mondriaan, exchangeability of exposure at different control windows

THIN HF-C1 & HF-C4										
Case	C1				Total	Case	C4			
	Current	Recent	Past				Current	Recent	Past	Total
Current	3,345	121	574		4,040	Current	2,446	102	1,036	3,584
Recent	312	21	91		424	Recent	162	19	191	372
Past	119	222	4,527		4,868	Past	377	160	3,890	4,427
Total	3,776	364	5,192		9,332	Total	2,985	281	5,117	8,383
Cases lacking control moment = 350					Cases lacking control moment = 1,299					
Discordancy		0.154			Discordancy		0.242			
Mondrian HF-C1 & HF-C4										
Case	C1				Total	Case	C4			
	Current	Recent	Past				Current	Recent	Past	Total
Current	92	4	25		121	Current	58	1	40	99
Recent	12	0	0		12	Recent	4	0	6	10
Past	4	5	118		127	Past	15	7	90	112
Total	108	9	143		260	Total	77	8	136	221
Cases lacking control moment = 17					Cases lacking control moment = 39					
Discordancy		0.192			Discordancy		0.330			

Appendix Table 3. Sensitivity analysis SCCS on evaluating pre-exposure periods

	THIN					
	Cases		Age adjusted	Cases		Age adjusted
	<i>N</i>	<i>PY</i>	<i>IRR (95% CI)</i>	<i>N</i>	<i>PY</i>	<i>IRR (95% CI)</i>
	<i>Pre-exposure period: 15 days</i>			<i>Pre-exposure period: 30 days</i>		
Past/non use (baseline)	5,177	39,123	-	5,066	38,602	-
Pre-exposed	136	843	1.04 (0.87 - 1.24)	270	1,528	1.16 (1.03 - 1.32)
Current	4,379	21,934	1.40 (1.32 - 1.49)	4,379	21,934	1.42 (1.34 - 1.51)
Recent	401	1,893	1.39 (1.26 - 1.55)	378	1,729	1.44 (1.29 - 1.60)
	<i>Pre-exposure period: 45 days</i>			<i>Pre-exposure period: 60 days</i>		
Past/non use (baseline)	4,955	38,122	-	4,820	37,666	-
Pre-exposed	398	2,119	1.26 (1.13 - 1.40)	558	2,655	1.45 (1.32 - 1.59)
Current	4,379	21,934	1.44 (1.36 - 1.53)	4,379	21,934	1.48 (1.40 - 1.58)
Recent	361	1,618	1.47 (1.32 - 1.64)	336	1,538	1.46 (1.30 - 1.63)

Appendix Table 4. Sensitivity analyses SCCS in THIN: evaluating various levels of right censoring at event

THIN		
Proportion censored at event	Age adjusted*	
	Current	Recent
0%	1.59 (1.59 - 1.59)	1.45 (1.45 - 1.45)
2%	1.61 (1.60 - 1.61)	1.46 (1.46 - 1.47)
5%	1.63 (1.62 - 1.64)	1.48 (1.47 - 1.49)
10%	1.67 (1.65 - 1.69)	1.51 (1.50 - 1.53)
20%	1.76 (1.73 - 1.79)	1.58 (1.55 - 1.60)
50%	2.12 (2.07 - 2.17)	1.82 (1.78 - 1.86)
100%	3.54 (3.54 - 3.54)	2.67 (2.67 - 2.67)

*Confidence intervals represent the variability when randomly censoring patients
 * 10 years age band used to make the model converged (this explains the difference in point estimate with the main analysis when 0% of patients are censored)*