

SUPPLEMENTARY MATERIAL

Supplementary Table 1 Inclusion and exclusion criteria

	Drug-induced colitis (DiC)	Non-inflammatory controls (NiC)	Inflammatory controls (IC)
Inclusion	In-patient receiving complete colonoscopy including biopsy samples		
	Histopathological pattern consistent with drug-induced colitis	No relevant histopathological changes, i.e. patients with irritable bowel syndrome	Histopathological confirmation of inflammatory activity other than drug-induced, i.e. inflammatory bowel disease, diverticulitis, ischemia etc.
Exclusion	Insufficient clinical data Incomplete drug history		
	Histopathological changes other than drug-induced colitis	Any relevant histopathological alteration	

Supplementary Table 2 Overview of drug classification

Group	Examples
Beta-blockers	Metoprolol, bisoprolol
ACE inhibitors	Ramipril, enalapril

Angiotensin II inhibitors	Losartan, candesartan
Non-dihydropyridines	Verapamil, diltiazem
Dihydropyridines	Nifedipine, amlodipine
Diuretics	Furosemid, torasemid
Benzothiazines	Dihydrochlorothiazid
Aldosterone antagonists	Spironolacton
Nitrates	Isosorbidmononitrat, isosorbiddinitrat, molsidomin
Antiarrhythmic drugs	Amiodaron, lidocain
Glycosides	Digitoxin, digoxin
ASS (100 mg to 300 mg)	ASS
Thrombocyte aggregation inhibitors	Clopidogrel
NSAIDs	ASS >300mg, ibuprofen, Diclofenac
Metamizole	Metamizole
Potassium	Potassium
Vitamin K antagonists / Coumarin derivatives	Phenprocoumon
Direct thrombin inhibitors	Dabigatran, apixaban, rivaroxaban
Glucocorticosteroids	Prednison, prednisolon, dexamethason
Opioids	Morphin, piritramid, fentanyl, sufentanil
Metformin	Metformin
Insulin	Insulin (human), actrapid, insulin glargin, Insulin isophan,
Statins	Simvastatin, pravastatin

Fibrates	Bezafibrat, clofibrat, etofibrat, fenofibrat, gemfibrozil
Levothyroxine	Levothyroxine
Thyreostatics	Carbimazol, thiamazol
Proton pump inhibitors	Pantoprazol, omeprazol, esomeprazol
Penicillin derivatives	Amoxicillin, piperacillin,
Makrolides	Erythromycin, roxithromycin
Gyrase inhibitor	Ciprofloxacin, levofloxacin
Carbapenems	Impenem, meropenem
Imidazoles	Metronidazol
Cephalosporins	Cefuroxim, ceftriaxon, ceftazidim
SSRIs	Fluoxetin, paroxetin, citalopram, sertraline
Tricyclic antidepressants	Amitriptylin, doxepin, trimipramin, imipramin, desipramin
Neuroleptics	Sulpirid, risperidon, reserpine, pipamperon, olanzapin, quetiapin
Sedatives	Diazepam, flunitrazepam, midazolam
Others	Laxatives (i.e. bisacodyl), antiemetics (i.e. dimenhydrinate), 5-aminosalicylate (i.e. mesalamine), selective antagonist at alpha-1A and alpha-1B-adrenoceptors (i.e. tamsulosin), immunomodulators (i.e. azathioprin), oral

	antikontraceptives, ursodesoxycholic acid, prokinetics (i.e. metoclopramide)

**Supplementary Table 3** Matching parameter results

Matching parameter	Drug-induced colitis n=211 (%)	Non-inflammatory controls n=211 (%)	Inflammatory controls n=211 (%)	p-value
Age (years), mean (SD)	62.3 ± 16.4	62.2 ± 16.3	61.8 ± 15.7	.940 <sup>a</sup>
Gender (male)	97 (46.0)	97 (46.0)	97 (46.0)	1.000 <sup>b</sup>
a: ANOVA				
b: $\chi^2$ test				

**Supplementary Table 4** Histopathological assessment

Parameter	DiC n=211 (%)	NiC n=211 (%)	IC n=211 (%)	DiC vs. IC	DiC vs. NiC	NiC vs. IC
Ischaemia	1 (0.5%)	0 (0.0%)	11 (5.2%)	.003a	.317a	.001a
Pseudomelanosis	3 (1.4%)	1 (0.5%)	0 (0.0%)	.082a	.315a	.317a
Lymphoplasmacellular and granulocyte infiltration	201 (95.3%)	85 (40.3%)	184 (87.2%)	.003a	< .001a	< .001a
Necrosis	7 (3.3%)	0 (0.0%)	14 (6.6%)	.117a	.008a	< .001a
Ulcer	16 (7.6%)	1 (0.5%)	31 (14.7%)	.020a	< .001a	< .001a

Regenerative hyperplasia of the crypts	26 (12.3%)	4 (1.9%)	26 (12.3%)	1.000a	< .001a	< .001a
Eosinophilia	52 (24.6%)	13 (8.2%)	42 (19.9%)	.242a	< .001a	< .001a
Oedema	51 (24.2%)	11 (5.2%)	51 (24.2%)	1.000a	< .001a	< .001a
Erosion	75 (35.5%)	8 (3.8%)	75 (35.5%)	1.000a	< .001a	< .001a
Subepithelial hemorrhage	39 (18.5%)	12 (5.7%)	30 (14.2%)	.236a	< .001a	.003a
Mucosal fibrosis	59 (28.0%)	31 (14.7%)	46 (21.8%)	.143a	.001a	.059a
Hyperplasia of the crypts	21 (10.0%)	8 (3.8%)	17 (8.1%)	.496a	.012a	.063a
Other	2 (0.9%)	1 (0.5%)	8 (3.8%)	.055a	.562a	.018a
<b>DiC:</b> drug-induced colitis, <b>NiC:</b> non-inflammatory controls, <b>IC:</b> inflammatory controls. a: X2 test, b: ANOVA, c: t-test.						

**Supplementary Table 5** Degree of inflammation among the reassessment groups

Inflammatory activity (n=28)	Drug-induced colitis without atherosclerosis	Drug-induced colitis with atherosclerosis	Ischaemic colitis
Mild	25 (89.3 %) ** <sup>γ</sup> □	23 (82.1 %)	10 (35.7 %) ** <sup>δ</sup> □

Moderate	1 (3.6 %) ** $\Upsilon$ □	3 (10.7 %)	9 (32.1 %) ** $\delta$ □
Severe	2 (7.1 %) ** $\Upsilon$ □	2 (7.1 %)	9 (32.1 %) ** $\delta$ □
<p>Statistical analysis was carried out with <math>\chi^2</math> test.</p> <p>*: significant with p &lt; .05</p> <p>**: significant with p &lt; .01</p> <p>†: drug-induced colitis without atherosclerosis vs. drug-induced colitis with atherosclerosis</p> <p><math>\Upsilon</math>□: drug-induced colitis without atherosclerosis vs. ischaemic colitis</p> <p><math>\delta</math>□: drug-induced colitis with atherosclerosis vs. ischaemic colitis</p>			

**Supplementary Table 6 Inflammation site among the reassessment groups**

Location (n=28)	Drug-induced colitis without atherosclerosis	Drug-induced colitis with atherosclerosis	Ischaemic colitis
Coecum / ileocecal valve	8 (28.6 %)	12 (42.9 %)	4 (14.3 %) * $\delta$ □
Ascending colon	14 (50.0 %) ** $\Upsilon$ □	10 (35.7 %)	3 (10.7 %) * $\delta$ □
Transverse colon	6 (21.4 %)	4 (14.3 %)	4 (14.3 %)
Descending colon	6 (21.4 %)	6 (21.4 %)	9 (32.1 %)
Sigmoid colon	13 (46.4 %)	10 (35.7 %)	16 (57.1 %)
Rectum	8 (28.6 %)	7 (25.0 %)	8 (28.6 %)

<p>Statistical analysis was carried out with <math>\chi^2</math> test.</p> <p>*: significant with <math>p &lt; .05</math></p> <p>**: significant with <math>p &lt; .01</math></p> <p>†: drug-induced colitis without atherosclerosis vs. drug-induced colitis with atherosclerosis</p> <p>‡: drug-induced colitis without atherosclerosis vs. ischaemic colitis</p> <p>§: drug-induced colitis with atherosclerosis vs. ischaemic colitis</p>	
---	--

**Supplementary Table 7** Drug distribution among the reassessment groups

Group	DiC without atherosclerosis n = 28	DiC with atherosclerosis n = 28	Ischaemic colitis n = 28
Betablocker	13 (46.4 %)	20 (71.4 %)	18 (64.3 %)
ACE inhibitors	12 (42.9 %)	14 (50.0 %)	18 (64.3 %)
Angiotensin II inhibitors	2 (7.1 %)	4 (14.3 %)	0 (0.0 %)
Non-Dihydropyridines	0 (0.0 %)	0 (0.0 %)	1 (3.6 %)
Dihydropyridines	4 (14.3 %)	9 (32.1 %)	7 (25.0 %)
Diuretics	12 (42.9 %)	11 (39.3 %)	10 (30.3 %)
Benzothiazines	7 (25.0 %)	5 (18.9 %)	4 (14.3 %)
Aldosterone antagonists	1 (3.6 %)	4 (14.3 %)	4 (14.3 %)
Nitrates	2 (7.1 %)	3 (10.7 %)	3 (10.7 %)
Antiarrhythmic drugs	0 (0.0 %)	3 (10.7 %)	1 (3.6 %)
Glycosides	3 (10.7 %)	3 (10.7 %)	2 (7.1 %)

ASS (100 mg to 300 mg)	10 (35.7 %)	16 (57.1 %)	13 (46.4 %)
Platelet aggregation inhibitors	0 (0.0 %)	2 (7.1 %)	2 (7.1 %)
NSAIDs	3 (10.7 %)	1 (3.6 %)	1 (3.6 %)
Metamizole	3 (10.7 %)	4 (14.3 %)	6 (21.4 %)
Vitamin K antagonists / Coumarin derivatives	2 (7.1 %)	4 (14.3 %)	4 (14.3 %)
Direct thrombin inhibitors	0 (0.0 %)	3 (10.7 %)	0 (0.0 %)
Metformin	1 (3.6 %)	2 (7.1 %)	2 (7.1 %)
Insulin	1 (3.6 %)	4 (14.3 %)	3 (10.7 %)
Statins	3 (10.7 %) **†	17 (60.7 %) ** <sup>†</sup> □	13 (46.4 %)
Fibrates	1 (3.6 %)	0 (0.0 %)	0 (0.0 %)
Others	19 (67.9 %)	18 (64.3 %)	18 (64.3 %)
Number of drugs <sup>b</sup>	4.8 ± 2.5 *†	6.6 ± 2.3 ** <sup>†</sup> □	6.6 ± 4.1

Statistical analysis was carried out with Fisher's exact test or t-test, as appropriate.

\*: significant with  $p < .05$ . \*\*: significant with  $p < .01$

a:  $p = 0.051$

†: DiC without atherosclerosis vs. ischaemic colitis

□: DiC without atherosclerosis vs. DiC with atherosclerosis



□:            DiC            with  
 atherosclerosis            vs.  
 ischaemic colitis