

# Supplemental Material

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**Table S1:** Overview of codes used to define study population, co-medication, and comorbidity

Category	Codes
<u>Study population</u>	
Infective endocarditis (first-time event)	ICD-10: DI33, DI38, DI398; ICD8: 421
Surgery during admission	<u>NOMESCO</u>
<i>Aortic valve</i>	Bioprostheses: KFMD10, KFCA70 Mechanical prostheses: KFMD00, KFCA60 Other valve prostheses: KFMD20, KFMD30, KFMD33, KFMD96
<i>Mitral valve</i>	KFK
<i>Pulmonic valve</i>	KFJB, KFJC, KFJE, KFJF, KFJW
<i>Tricuspid valve</i>	KFG
<u>Comorbidity/previous intervention (prior to index date)</u>	
Aortic valve disease	ICD-10: I35s ICD-8: 395, 396
Atrial flutter/fibrillation	ICD-10: DI48, ICD-8:42793, 42794
Chronic obstructive lung disease (COPD)	ICD-10: DJ42-44 ICD-8: 490-492
Chronic kidney disease (CKD)	ICD-10: DN02-08, DN11-12, DN14, DN18-19, DN26, DN158-160, DN162-164, DN168, DQ612-613, DQ615, DQ619, DE102, DE112, DE132, DE142, DI120, DI131, DM300, DM313, DM319, DM321, DZ992 ICD-8: 403-404, 581-584, 25002, 40039, 59009, 59320, 75310, 754311, 75319
CIED	NOMESCO: BFCA0, BFCB0
Diabetes mellitus	ICD-10: DE10-14 ICD-8: 250 ATC code: A10
Heart failure	ICD10: DI42, DI50, DI099, DI110, DI130, DI132, DJ819 ICD-8: 425, 428, 4270, 4271, 78249
Ischemic heart disease (IHD)	ICD-10: DI20-25 ICD-8: 410-414
<i>PCI</i>	NOMESCO: KFNG0, KFNG10, KFNG12, KFNG96
<i>CABG</i>	NOMESCO: KFNA, KFNB, KFNC, KFNC, KFNE
Liver disease	ICD-10: DB15-19, DK70-77, DC22, DI982, DZ944, DD684C, DQ618A, ICD-8: 571-573, 155, 070
Malignancy	ICD-10: DC00-97, not including C44 (skin cancer) ICD-8: 140-209, not including 173 (skin cancer)
Mitral valve disease	ICD-10: I34

Prosthetic heart valve	ICD-8: 394, 396
Renal dialysis	KFKD, KFMD, KFGE, KFJF, KFCA60, KFCA70
	ICD-10: DZ992
	NOMESCO: BFJD2
<u>Pharmacotherapy (within 6 months prior to index date)</u>	
Anticoagulants (DOAC and VKA)	ATC code: B01AA, B01AE, B01AF
Beta blockers	ATC code: C07, C09BX
Lipid-lowering medication	ATC code: C10
RAS-inhibitors	ATC code: C09
<u>Hypertension</u>	<i>Defined as two or more antihypertensive drugs within 6 months prior to index data including the following:</i>
<i>Adrenergic antagonists</i>	ATC code: C02A, C02B, C02C
<i>Beta blockers</i>	ATC code: C07, C09BX
<i>Calcium channel blockers</i>	ATC code: C08, C07F, C09BB, C09DB
<i>Combined diuretics</i>	ATC code: C07C, C08G, C03B, C09BA, C09DA
<i>Loop-diuretics</i>	ATC code: C03C, C03EB01, C03EB02
<i>MRA</i>	ATC code: C03DA01-C03DA04
<i>RAS-inhibitors</i>	ATC code: C09
<i>Thiazide diuretics</i>	ATC code: C03A, C07B, C07D, C09XA52, C03EA01
<i>Vasodilating drugs</i>	ATC code: C02DB, C02DD, C02DG

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ICD: international classification of diseases, ATC: Anatomical Therapeutical Classification System, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CIED: cardiac implantable electronic device, DOAC: direct oral anticoagulant therapy, MRA: aldosterone receptor antagonists, RAS: renin angiotensin system, VKA: vitamin K antagonists

**Table S2a:** *Streptococcus* species - distribution on species level

Microorganism	Counts	Percent
<b>Non-hemolytic streptococci</b>		
<b><i>S. anginosus</i> / <i>S. milleri</i> group</b>		
<i>S. anginosus</i>	67	2.82
<i>S. milleri</i>	13	0.74
<i>S. constellatus</i>	4	0.23
<i>S. intermedius</i>	6	0.34
<b><i>S. bovis</i> / <i>equinus</i> group</b>		
<i>S. bovis</i>	163	9.30
<i>S. gallolyticus</i>	39	2.23
<i>S. infantarius</i>	7	0.40
<b><i>S. mitis</i> group</b>		
<i>S. mitis</i>	385	21.97
<i>S. gordonii</i>	36	2.05
<i>S. oralis</i>	33	1.88
<i>S. parasanguinis</i>	10	0.57
<i>S. sanguinis</i>	108	6.16
<i>S. pneumoniae</i>	77	4.39
<i>S. salivarius</i>	55	3.14
<i>S. mutans</i>	98	5.59
<b>Non-hemolytic streptococci unspecified</b>	116	6.62
<b>Hemolytic streptococci</b>		
Hemolytic streptococci unspecified	43	2.45
<i>Hemolytic streptococci group A</i>	32	1.83
<i>Hemolytic streptococci group B</i>	149	8.50
<i>Hemolytic streptococci group C</i>	60	3.42
<i>Hemolytic streptococci group G</i>	133	7.59
<i>Streptococcus dysgalactiae</i>	33	1.88
<b>Other</b>		
<i>Abiotrophia defectiva</i>	23	1.31
<i>Gemella haemolysans</i>	5	0.29
<i>Granulicatella adiacens</i>	17	0.97
<i>Granulicatella elegans</i>	4	0.23
Streptococcus species unspecified	36	2.05

**Table S2b:** Coagulase-negative Staphylococci - distribution on species level

<b>Microorganism</b>	<b>Counts</b>	<b>Percent</b>
Bacteria anonymized due to count below 3	4	0.97
<i>Staphylococcus capitis</i>	28	6.76
<i>Staphylococcus epidermidis</i>	243	58.70
<i>Staphylococcus haemolyticus</i>	12	2.90
<i>Staphylococcus hominis</i>	25	6.04
<i>Staphylococcus lugdunensis</i>	43	10.39
<i>Staphylococcus species unspecified</i>	55	13.29
<i>Staphylococcus warneri</i>	4	0.97

**Table S2c:** Other microbiological causes - distribution on species level

<b>Microorganism</b>	<b>Count</b>	<b>Percent</b>
<b>HACAK</b>		
<i>Haemophilus parainfluenzae</i>	13	3.98
<i>Aggregatibacter aphrophilus</i>	8	2.45
<i>Aggregatibacter actinomycetemcomitans</i>	17	5.2
<i>Cardiobacterium hominis</i>	13	3.98
<i>Cardiobacterium species</i>	3	0.92
<i>Kingella kingae</i>	5	1.53
<b>Gram-positive bacteria</b>		
<i>Aerococcus species</i>	4	1.22
<i>Aerococcus urinae</i>	29	8.87
<i>Corynebacterium striatum</i>	4	1.22
<i>Lactocaseibacillus rhamnosus</i>	3	0.92
<i>Lactocaseibacillus species</i>	3	0.92
<i>Listeria monocytogenes</i>	6	1.83
<i>Micrococcus species</i>	3	0.92
<i>Rothia dentocariosa</i>	3	0.92
<b>Gram-negative bacteria</b>		
<i>Enterobacter cloacae</i>	8	2.45
<i>Escherichia coli</i>	40	12.23
<i>Haemophilus influenzae</i>	5	1.53
<i>Klebsiella oxytoca</i>	9	2.75
<i>Klebsiella pneumoniae</i>	15	4.59
<i>Pseudomonas aeruginosa</i>	12	3.67
<i>Serratia marcescens</i>	8	2.45
<b>Anaerobic</b>		
<i>Bacteroides fragilis</i>	3	0.92
<i>Cutibacterium acnes</i>	21	6.42
<b>Fungus</b>		
<i>Candida albicans</i>	8	2.45
<i>Candida glabrata</i>	5	1.53
<b>Unspecified</b>	13	3.98
<b>Bacteria anonymized due to count below 3</b>	66	20.18

**Table S3:** Frequencies and proportions of the heart valves replaced in the surgical treated patients

<b>Surgical valve replacements</b>	<b>Numbers</b>	<b>Proportion (%)</b>
<b>Left-sided valves</b>	<b>1184</b>	<b>92.79</b>
Isolated aortic valve <sup>a</sup>	632	53.38
Isolated mitral valve <sup>a</sup>	343	28.97
Combined (aortic and mitral valves) <sup>a</sup>	209	17.65
<b>Right-sided valves</b>	<b>31</b>	<b>2.43</b>
<b>Combined left -and right-sided valves</b>	<b>61</b>	<b>4.78</b>
Aortic valve and right-sided valves <sup>b</sup>	28	45.90
Mitral valve and right-sided valves <sup>b</sup>	13	21.31
Both aortic and mitral valves and right-sided valves <sup>b</sup>	20	32.79

<sup>a</sup>Frequencies and proportions of left-sided valve replacements. The percentages add up to 100% of all 1184 solely left-sided valve replacements.

<sup>b</sup>Frequencies and proportions of combined left -and right-sided valve replacements. The percentages add up to 100% of all 66 combined left -and right-sided valve replacements.



**Table S4:** Baseline characteristics in the age -and sex-matched cohort stratified by treatment choice

Variable	Medical therapy only, N = 1270 <sup>a</sup>	Surgery during admission, N = 1270 <sup>a</sup>
Males	973 (76.6)	973 (76.6)
Age	65 [54-72]	65 [54-72]
Length of hospital stay (days)	36 [26-48]	46 [35-58]
Length of hospital stay among patients alive at discharge (days)	41 [30-49]	46 [39-59]
Microbiological etiology		
<i>Staphylococcus aureus</i>	478 (37.6)	262 (20.6)
<i>Streptococcus</i>	310 (24.4)	444 (35.0)
<i>Enterococcus</i>	153 (12.0)	183 (14.4)
CoNS	93 (7.3)	91 (7.2)
Other	60 (4.7)	77 (6.1)
Negative	176 (13.9)	213 (16.8)
Prosthetic heart valve	210 (16.5)	246 (19.4)
Cardiac implantable electrical devices (CIED)	235 (18.5)	70 (5.5)
Aortic valve disease	253 (19.9)	362 (28.5)
Mitral valve disease	82 (6.5)	124 (9.8)
Atrial fibrillation (AF)	253 (19.9)	189 (14.9)
Heart failure (HF)	231 (18.2)	155 (12.2)
Ischemic heart disease (IHD)	334 (26.3)	226 (18.8)
Cerebrovascular disease (CVD)	176 (13.9)	149 (11.7)
Dementia	14 (1.1)	≤3
Hypertension	622 (49.0)	512 (40.3)
Chronic kidney disease (CKD)	137 (10.8)	78 (6.1)
Dialysis	91 (7.2%)	53 (4.2)
Diabetes	309 (24.3)	202 (15.9)
Liver disease	114 (9.0)	35 (2.8)
Chronic obstructive pulmonary disease (COPD)	128 (10.1)	76 (6.0)
Charlson comorbidity index		

**Table S4:** Baseline characteristics in the age -and sex-matched cohort stratified by treatment choice

Variable	Medical therapy only, N = 1270 <sup>a</sup>	Surgery during admission, N = 1270 <sup>a</sup>
0	454 (35.7)	704 (55.4)
1-2	432 (34.0)	412 (32.4)
>2	384 (30.2)	154 (12.1)
Anticoagulants	322 (25.4)	260 (20.5)
Beta blockers	481 (37.9)	336 (26.5)
Lipid-lowering medication	462 (36.4)	409 (32.2)
RAS inhibitors	498 (39.2)	464 (36.5)

<sup>a</sup>Median [25th.75th percentile] or Frequency (%)

**Table S5:** Baseline characteristics stratified by microbiological etiology in patients who underwent surgery.

Variable	<i>S. aureus</i> , N = 262 <sup>a</sup>	<i>Streptococcus</i> spp., N = 447 <sup>a</sup>	<i>Enterococcus</i> spp., N = 183 <sup>a</sup>	CoNS, N = 92 <sup>a</sup>	Other, N = 77 <sup>a</sup>	Negative, N = 215 <sup>a</sup>
Males	180 (68.7%)	349 (78.1%)	153 (83.6%)	67 (72.8%)	65 (84.4%)	159 (74.0%)
Age	61.0 [49.0- 70.0]	64.0 [55.0- 71.5]	71.0 [64.0- 76.0]	65.5 [57.0- 73.0]	64.0 [53.0- 71.0]	62.0 [51.0- 71.5]
Length of hospital stay (days)	51.0 [43.0- 67.0]	43.0 [32.0- 51.0]	50.0 [44.0- 65.0]	46.0 [42.0- 58.2]	47.0 [34.0- 60.0]	45.0 [31.5- 54.0]
Prior valve prosthesis	46 (17.6%)	67 (15.0%)	39 (21.3%)	33 (35.9%)	13 (16.9%)	50 (23.3%)
Cardiac implantable electrical devices (CIED)	15 (5.7%)	5 (1.1%)	23 (12.6%)	7 (7.6%)	7 (9.1%)	13 (6.0%)
Aortic valve disease	52 (19.8%)	99 (22.1%)	70 (38.3%)	37 (40.2%)	26 (33.8%)	78 (36.3%)
Mitral valve disease	16 (6.1%)	35 (7.8%)	14 (7.7%)	20 (21.7%)	6 (7.8%)	33 (15.3%)
Atrial fibrillation (AF)	35 (13.4%)	56 (12.5%)	31 (16.9%)	26 (28.3%)	12 (15.6%)	29 (13.5%)
Heart failure (HF)	25 (9.5%)	33 (7.4%)	33 (18.0%)	24 (26.1%)	8 (10.4%)	33 (15.3%)
Ischemic heart disease (IHD)	38 (14.5%)	62 (13.9%)	50 (27.3%)	19 (20.7%)	15 (19.5%)	42 (19.5%)
Hypertension	109 (41.6%)	142 (31.8%)	96 (52.5%)	41 (44.6%)	27 (35.1%)	97 (45.1%)
Chronic kidney disease (CKD)	31 (11.8%)	12 (2.7%)	9 (4.9%)	12 (13.0%)	4 (5.2%)	10 (4.7%)
Dialysis	26 (9.9%)	3 (0.7%)	7 (3.8%)	11 (12.0%)	≤3 (<4.0%)	5 (2.3%)

**Table S5:** Baseline characteristics stratified by microbiological etiology in patients who underwent surgery.

Variable	<i>S. aureus</i> , N = 262 <sup>a</sup>	<i>Streptococcus</i> spp., N = 447 <sup>a</sup>	<i>Enterococcus</i> spp., N = 183 <sup>a</sup>	CoNS, N = 92 <sup>a</sup>	Other, N = 77 <sup>a</sup>	Negative, N = 215 <sup>a</sup>
Diabetes	46 (17.6%)	65 (14.5%)	33 (18.0%)	16 (17.4%)	13 (16.9%)	29 (13.5%)
Liver disease	10 (3.8%)	12 (2.7%)	3 (1.6%)	4 (4.3%)	3 (3.9%)	3 (1.4%)
Chronic obstructive pulmonary disease (COPD)	16 (6.1%)	19 (4.3%)	14 (7.7%)	6 (6.5%)	≤3 (<4.0%)	19 (8.8%)
Anticoagulants	47 (17.9%)	68 (15.2%)	55 (30.1%)	29 (31.5%)	20 (26.0%)	41 (19.1%)
Beta blockers	72 (27.5%)	87 (19.5%)	58 (31.7%)	36 (39.1%)	22 (28.6%)	61 (28.4%)
Lipid-lowering medication	80 (30.5%)	137 (30.6%)	78 (42.6%)	33 (35.9%)	22 (28.6%)	59 (27.4%)
RAS inhibitors	101 (38.5%)	141 (31.5%)	86 (47.0%)	35 (38.0%)	25 (32.5%)	76 (35.3%)

<sup>a</sup>Median [25th.75th percentile] or Frequency (%)

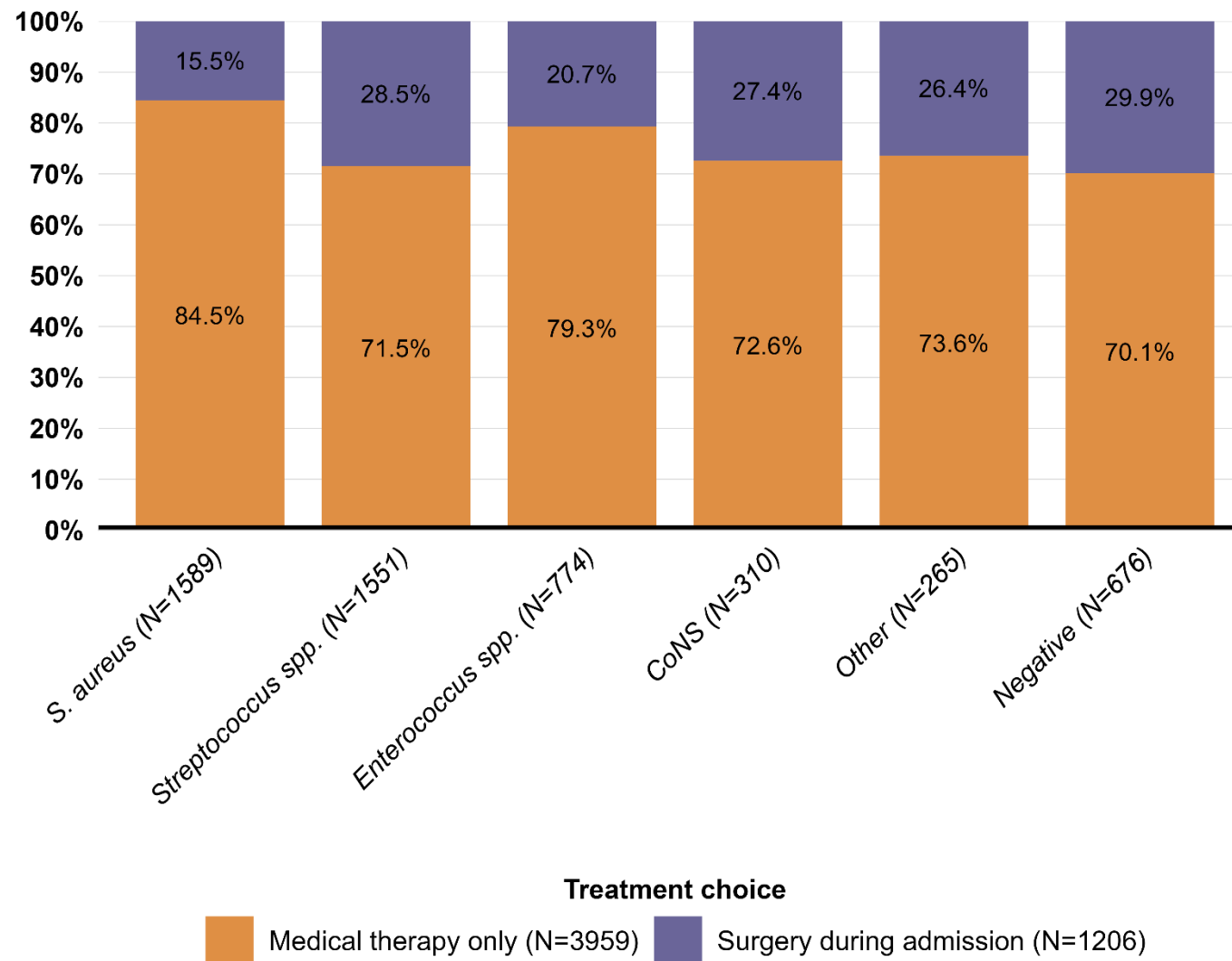
**Table S6:** Overview of status at discharge (alive or dead) in numbers and percentages according to microbiological etiology and treatment choice

	<i>S. aureus</i> (N=1924)	<i>Streptococcus</i> spp. (N=1752)	<i>Enterococcus</i> spp. (N=982)	CoNS (N=414)	Other (N=327)	Negative (N=856)	Total (N=6255)
Surgery and death during admission	48 (2.5%)	50 (2.8%)	20 (2.0%)	9 (2.2%)	9 (2.8%)	19 (2.2%)	155 (2.5%) (12.1%)*
Surgery and alive at discharge	214 (11.1%)	397 (22.7%)	163 (16.6%)	83 (20.1%)	68 (20.8%)	196 (22.9%)	1121 (17.9%) (87.9%)*
Medical therapy and death during admission	489 (25.4%)	161 (9.2%)	147 (15.0%)	76 (18.4%)	40 (12.2%)	131 (12.6%)	1044 (16.7%) (21.0%)**
Medical therapy and alive at discharge	1173 (61.0%)	1144 (65.3%)	652 (66.4%)	246 (59.4%)	210 (64.2%)	510 (59.6%)	3935 (62.9%) (79.0%)**

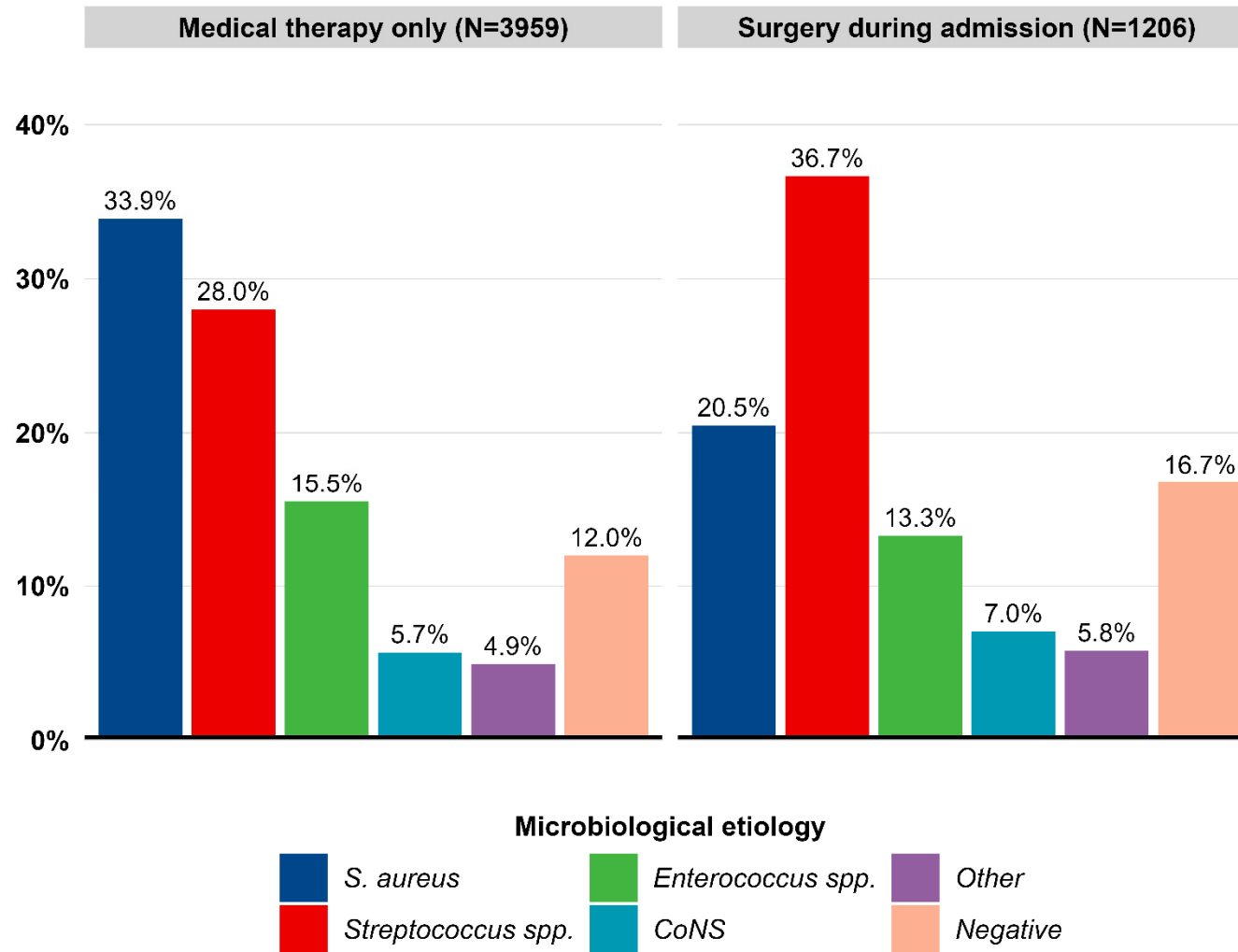
\*Out of all patients who underwent surgery during admission (N=1276)

\*\* Out of all patients who received medical therapy only (N=4979)

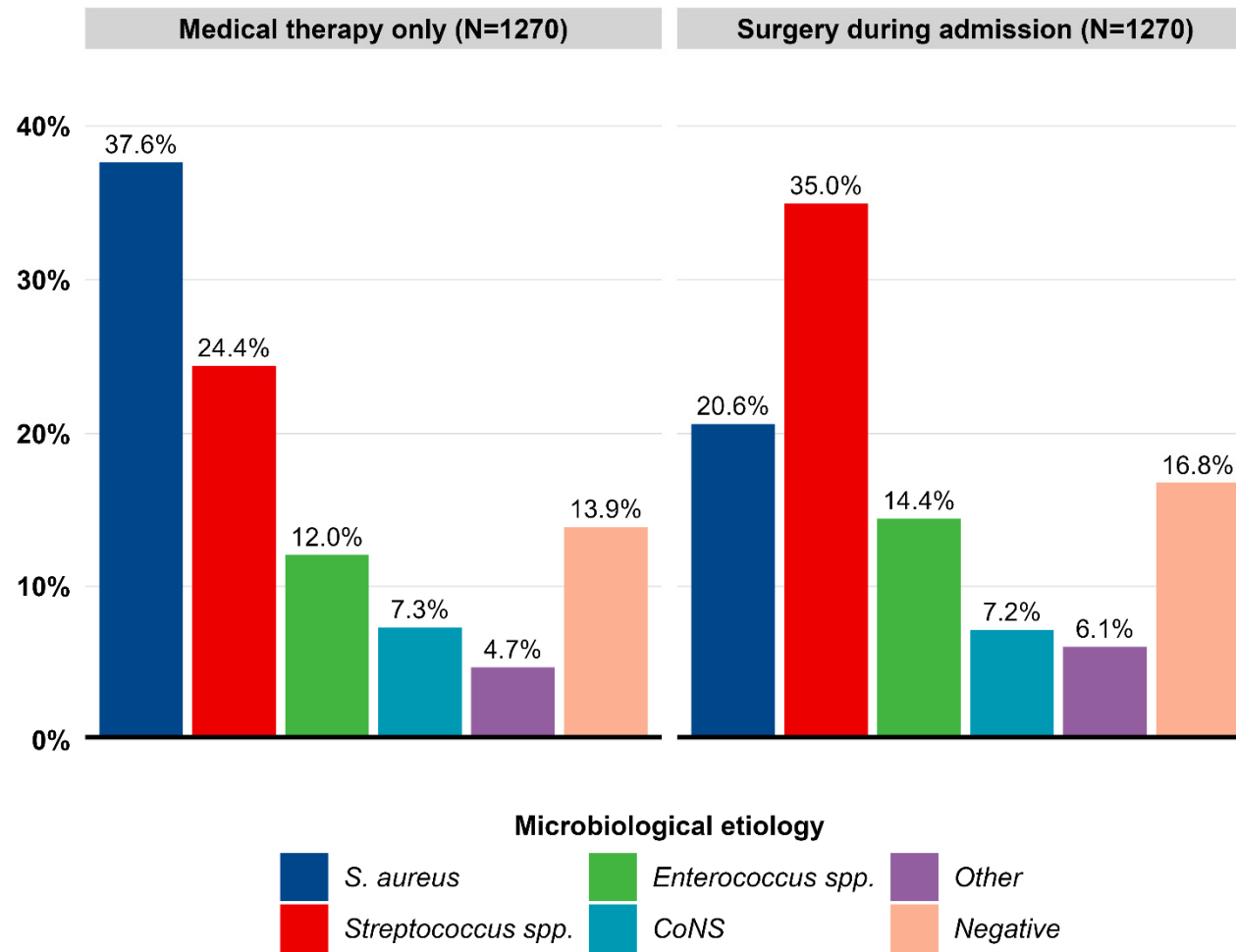
**Figure S1:** Proportion of treatment choice stratified by microbiological etiologies after exclusion of CIED at baseline



**Figure S2:** Proportion of microbiological etiologies stratified by treatment choice (surgery during admission vs. medical therapy) after exclusion of CIED at baseline

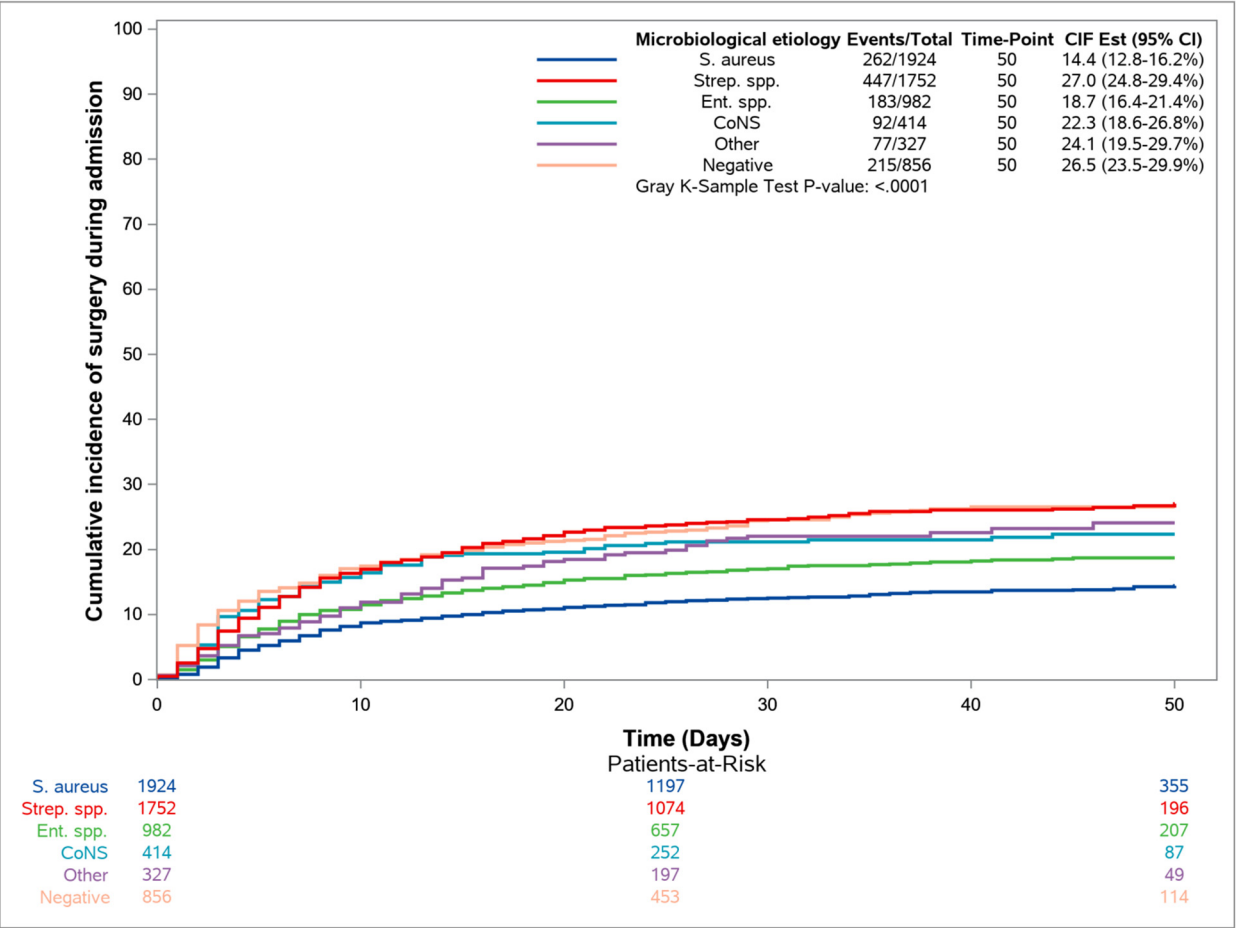


**Figure S3:** Proportion of microbiological etiologies stratified by treatment choice (surgery during admission vs. medical therapy) in an age – and sex-matched cohort





**Figure S4:** Cumulative incidence of surgery during admission stratified by microbiological etiology



**Figure S5A+B:** Mortality rates by microbiological etiology and treatment choice (surgery during admission vs. medical therapy) in an age -and sex-matched cohort.

