Supplementary appendix

Comparison of preoperative remission scores and diabetes duration alone as predictors of durable type 2 diabetes remission and risk of diabetes complications after bariatric surgery: a post-hoc analysis of participants from the Swedish Obese Subjects study

Kajsa Sjöholm, Lena MS Carlsson, Magdalena Taube, et al

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The Swedish Obese Subjects (SOS) study design

After recruitment campaigns in the mass media and at 480 primary health-care centers, a matching examination was completed by 6905 patients, 5335 of which were eligible. Among them, 2010 individuals electing surgery formed the surgery group, and a matched control group of 2037 individuals was contemporaneously created using 18 matching variables. The matching variables were sex, age, weight, height, waist and hip circumferences, systolic blood pressure, serum cholesterol and triglyceride levels, smoking status, diabetes, menopausal status, four psychosocial variables with documented associations with the risk of death, and two personality traits related to treatment preferences. A matching algorithm selected controls so that the current mean values of the matching variables in the control group became as similar as possible to the current mean values in the surgery group according to the method of sequential treatment assignment (1). The inclusion and exclusion criteria were identical for the two study groups, and all participants were eligible for surgery. The inclusion criteria were aged 37 to 60 years and BMI of 34 kg/m^2 or more for men and 38 kg/m^2 or more for women before or at the matching examination. The BMI cutoffs corresponded to an approximate doubling in the rate of death in men and women (2). The exclusion criteria were earlier surgery for gastric or duodenal ulcer, earlier bariatric surgery, gastric ulcer during the past 6 months, ongoing malignancy, active malignancy during the past 5 years, myocardial infarction during the past 6 months, bulimic eating pattern, drug or alcohol abuse, psychiatric or cooperative problems contraindicating bariatric surgery, other contraindicating conditions (such as chronic glucocorticoid or anti-inflammatory treatment). Patients were recruited between September 1, 1987, and January 31, 2001. The intervention began on the day of surgery for subjects in the surgery group and for their matched controls. The type of surgery was determined by surgeons at the participating surgical departments. No attempt was made to standardize the non-surgical treatment, which ranged from advanced life-style advice at some centers to no treatment in others. About four weeks before the start of the intervention, baseline examinations were done and follow up examinations were scheduled at 0.5, 1, 2, 3, 4, 6, 8, 10, 15 and 20 years. Blood samples were taken after an overnight fast at baseline and after 2, 10, and 15 years. From 1987 to 2009, glucose concentrations were measured in venous whole blood at the Central Laboratory, Sahlgrenska University Hospital, accredited according to ISO/IEC 189. After August 1, 2009, venous plasma glucose has been measured and converted to blood glucose according to the instructions from the Central Laboratory (blood glucose = plasma glucose / 1.12). The SOS study was started before repeated measurements were routinely used for the diagnosis of type 2 diabetes, and single determinations of fasting glucose or HbA1c, were therefore used. Self-reported medication and diabetes duration was obtained from SOS questionnaires.

sTable 1. Score prediction models

	ABCD (3)		**DiaRem** (4)		**Ad-DiaRem** (5)		**DiaBetter** (6)		**IMS**[a] (7)	
Prediction factor		**Score**		**Score**		**Score**		**Score**		**Score**
Age (y)	≥40	0	<40	0	15-41	0				
	<40	1	40-49	1	42-52	3				
			50-59	2	52-69	5				
			≥60	3						
BMI (kg/m^2)	<30	0								
	30-39	1								
	40-49	2								
	>50	3								
C-peptide (ng/ml)	0.9-1.9	0								
	2.0-3.9	1								
	4-6	2								
	>6	3								
HbA1C (mmol/mol (%))			<48 (6.5)	0	26 (4.5)- 52 (6.9)	0	≤48 (6.5)	0	<53 (7)	0
			≥48 (6.5) – ≤52 (6.9)	2	53 (7.0) -57 (7.4)	2	49 (6.6) - 55 (7.2)	1	≥53 (7)	16
			≥53 (7.0) - ≤74 (8.9)	4	58 (7.5) -178 (18.4)	4	56 (7.3) – 68 (8.4)	2		
			≥75 (9.0)	6	-	-	≥69 (8.5)	3		
Insulin treatment			No	0	No	0	No	0	No	0
			Yes	10	Yes	3	Yes (alone or in combination)	3	Yes	18
Metformin			Only metformin	0	Only metformin	0	Only metformin	1		
Other anti-diabetic drugs			SU and insulin sensitizing agents other than metformin	3	Other glucose lowering agents[b]	1	Only other non-insulin drug(s)	2		
Number of glucose-lowering agents[c]					0	0			0	0
					1	1			1	12.6
					2	2			2	25.2
					≥3	3			3	37.8
									4	50.4
									5	63
Diabetes Duration	>10	0			0-6.9	0	≤2	0	0	0

	5-10	1			7-13.9	3	2.1-5.0	1	1-2-3-4-5	5.6-11.2-16.8-22.4-28
	2-4.9	2			≥14	5	5.1-10.0	2	6-7-8-9-10	32-36-40-44-48
	<2	3			-		≥10.1	3	11-12-13-14-15	50-52-54-56-58
									16--40	59.68--100
Range of score		**0-10**		**0-22**		**0-21**		**0-9**		**0-197**

[a] For each additional duration year between 1-5 years, add 5.6 points; between 6-10 years, add 4 points; between 11-15 years, add 2 points; between 16-40 years, add 1.68 points.
[b] Includes sulfonylureas (glimepiride, glipizide and glibenclamide), insulin sensitizing agents other than metformin (pioglitazone and rosiglitazone).
[c] Includes sulfonylureas, insulin sensitizing agents and GLP-1 analogues, DDP-IV inhibitors, insulin and other glucose-lowering agents.

sTable 2. Non-fatal and fatal diabetes complications according to ICD-9 and ICD-10 and according to Surgical procedures as coded in the National Swedish Patient Register (with inpatient and specialist outpatient care) and Cause of Death Register.
Registry searches were performed using these codes and any sub-classifications thereof.

Diagnosis	**ICD-9**	**ICD-10**	**Surgical procedures**	**Procedure codes of National Swedish Board of Health and Welfare:** Classification of operations* Ed. 5, 1985 Ed. 6, 1989, both editions including also non-surgical procedures.	**Procedure codes of National Swedish Board of Health and Welfare:** Classification of surgical procedures (KKÅ) 1997 Temporary list of non-surgical procedures (TÅL) 1997. Swedish Classifications of Health Interventions (KVÅ) 2007† including both surgical (KKÅ) and non-surgical (KMÅ) procedures.
Microvascular diabetes complications, non-fatal or fatal					
Kidney complications	250D	E11.2 E10.2‡ E14.2	Kidney transplantation	6070	KAS00 KAS10 KAS20
			Kidney biopsy	6080	KAB00
Diabetes nephropathy		N08.3		6081	KAB01
Albuminuria	791A	R80 N39.1	Hemodialysis	9211 9212	DR015 DR016 DR020 V9211
Renal failure	584 to 586	N17 to N19			V9212
			Peritoneal dialysis	9213	DR023
Dialysis	V45B V56A V56W	Z99.2 Z49		9214	DR024 JAK10 TJA20 TJA33 V9213 V9214

Eye complications	250E	E11.3 E10.3‡ E14.3			
Diabetes retinopathy	250E	H36.0	Retinal operations	1630-1638	CKC CKD
Neurological complications	250F	E11.4 E10.4‡ E14.4			
Amyotrophy		G73.0			
Autonomous (poly)neuropathy	357E	G99.0			
Mononeuropathy		G59.0			
Polyneuropathy		G63.2			
Peripheral, mainly macrovascular diabetes complications, non-fatal and fatal§					
Claudication, atherosclerosis of arteries of extremities	443X 440C	I70.2	Amputations on leg or foot	8750 8760 8770 8771	NFQ NGQ NHQ
Diabetes gangrene, diabetic foot	250G	E11.5 E10.5‡		8780 8781	
Diabetes gangrene, cont.		E14.4 I79.2			
			Operations on suprarenal aorta and visceral arteries	0963 0964 0965	PCE PCF PCG PCH PCJ PCK PCN PCP PCQ
			Operations on renal aorta and iliac arteries	8836 8837 8838 8839	PDE PDF PDG PDH

				8884 8885 8815 8816 8817 8818	PDN PDP PDQ PDS
			Operations leg arteries	8861 8862 8865 8866 8868 8886 8887 8825 8826 8827 8828 8884 8885	PEE PEF PEG PEH PEN PEP PEQ PFE PFG PFH PFN PFP PFQ PFS
Macrovascular centrally located diabetes complications, non-fatal or fatal§					
Angina pectoris Acute myocardial infarction Myocardial reinfarction Complications to myocardial inf. Other ischemic conditions Heart failure	413 410 411 412 414 428	I20 I21 I22 I23 I24 I25 I50	Coronary artery operations Heart transplantation	3105 3127 3158 3085	FNA **to** FNK FNW FQA FQB
Subarachnoidal bleeding Hemorrhagia cerebri	430 431 432x	I60 I61 I62	Aneurysm operations Arterial operations	0190 0191 0193	AAC AAL PAF PAG

Cerebral infarction	434	I63			PAH PAJ
Unspecified stroke	436	I64			PAK

* First edition of Classification of Operations (Swedish: “Klassifikation av Operationer”) was printed by the National Swedish Board of Health and Welfare in 1963.
† KVÅ is available only online (www.socialstyrelsen.se/klassificeringochkoder/atgardskoderkva) and is updated annually since 2007. Older code lists were printed by the National Swedish Board of Health and Welfare.
‡ In the Swedish National Patient Registry and the Cause of Death Registry, complications of some typical type 2 diabetic individuals have erroneously been coded as type 1 diabetes (i.e. with E10# codes), particularly if they have obtained insulin treatment. Since we know that all patients in this report had type 2 diabetes at baseline (see Methods), we have included both E11 (type 2) and E10 (type 1) codes in our searches for complications of type 2 diabetes.
§ Since we know that all patients in this report had type 2 diabetes at the SOS baseline examination, we have considered claudication as well as heart and brain problems as diabetic complications even if diabetes is not a specified diagnosis in the corresponding hospital records.

sTable 3: Predictive capacity of scores and duration in relation to type of surgical procedure

		AUROC (95% CI)	
Outcome*	**Score/predictor**	**GBP†**	**Banding/VBG**
10-year remission	N	39	188
	ABCD	0.77 (0.63-0.92)	0.69 (0.61-0.77)
	DiaRem	0.72 (0.54-0.89)	0.72 (0.64-0.80)
	Ad-DiaRem	0.76 (0.60-0.92)	0.70 (0.62-0.78)
	DiaBetter	0.76 (0.60-0.91)	0.73 (0.65-0.81)
	IMS	0.77 (0.61-0.92)	0.75 (0.67-0.82)
	Diabetes duration	**0.77 (0.64-0.91)**	**0.71 (0.64-0.77)**
Microvascular complications	N	65	298
	ABCD	0.80 (0.58-1.00)	0.68 (0.59-0.77)
	DiaRem	0.83 (0.64-1.00)	0.76 (0.68-0.84)
	Ad-DiaRem	0.83 (0.64-1.00)	0.78 (0.71-0.85)
	DiaBetter	0.77 (0.51-1.00)	0.80 (0.73-0.86)
	IMS	0.80 (0.58-1.00)	0.79 (0.73-0.85)
	Diabetes duration	**0.80 (0.58-1.00)**	**0.76 (0.69-0.83)**
Macrovascular complications	N	65	298
	ABCD	0.61 (0.45-0.77)	0.62 (0.55-0.69)
	DiaRem	0.60 (0.43-0.77)	0.70 (0.64-0.77)
	Ad-DiaRem	0.64 (0.49-0.79)	0.71 (0.65-0.77)
	DiaBetter	0.56 (0.38-0.73)	0.68 (0.61-0.74)
	IMS	0.59 (0.42-0.76)	0.68 (0.61-0.74)
	Diabetes duration	**0.63 (0.47-0.78)**	**0.65(0.59-0.72)**

*Note that 2-year prediction of diabetes remission could not be performed due to very few non-remission cases at this timepoint.

†Prediction in the GBP subgroup should be interpreted with caution due to small numbers.

sTable 4. Youden empirical estimation of optimal score and duration cut-offs within the SOS surgery cohort*†

	ABCD		DiaRem		Ad-DiaRem		DiaBetter		IMS		Diabetes duration (years)‡	
Endpoint	Cut-off	Sens;Spec	Cut-off	Sens;Spec	Cut-off	Sens;Spec	Cut-off	Sens;Spec	Cut-off	Sens;Spec	Cut-off	Sens;Spec
2-year remission	≥6	81;70	≥7	76; 80	≥8	72; 82	≥4	78; 84	≥30	80;80	≥2	75;79
10-year remission	≥7	64;67	≥7	45; 84	≥6	64; 66	≥2	73; 63	≥17	58;81	≥1	61;80
Microvascular	≥5	88;49	≥8	67; 79	≥8	70; 77	≥5	67; 83	≥30	76;73	≥1	82;61
Macrovascular	≥6	72;46	≥8	52; 80	≥8	56; 78	≥4	52; 76	≥29	58;72	≥2	55;72

* Optimal SOS cut-offs to be compared with previously reported estimates of Youden score cut-offs for short-term (1-2 year) prediction of diabetes remission in cohorts of varying composition: ABCD cut-off 4 or 6; DiaRem score cut-off 5, 6, 7 or 8; Ad-DiaRem score cut-off 7 or 10; DiaBetter score cut-off 3; IMS cut-off 47 (5, 8-11).

† In the statistical analysis, the true positive condition was designated for non-remission or development of diabetes complications at specified score cut-offs.

‡ Note that due to the high proportion of patients with screen-detected diabetes in the SOS study, these cut-offs should be interpreted with caution, and validated with external cohorts, and thus not viewed upon as a clinically reliable cut-offs for treatment recommendations.

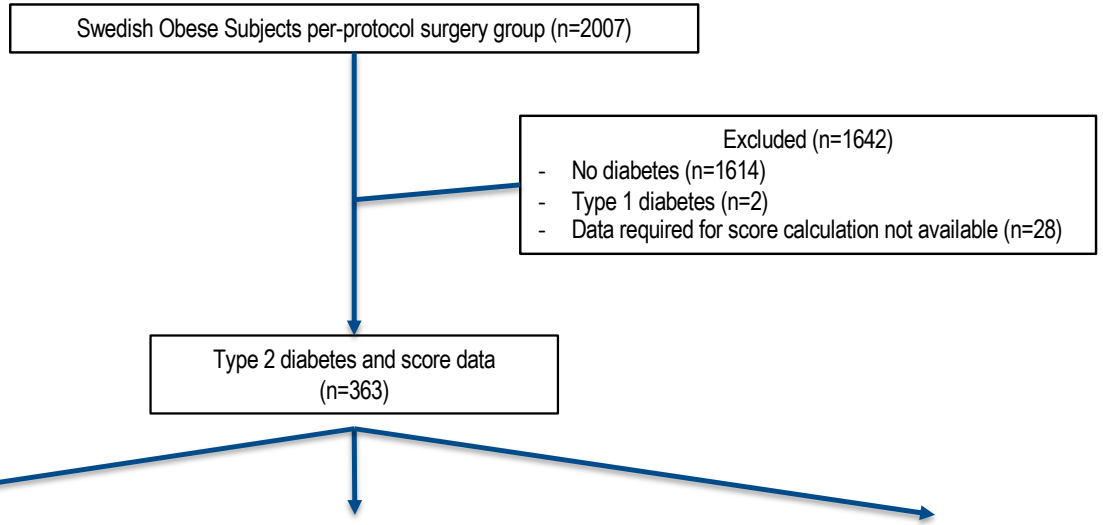
sTable 5. Derivation and validation of risk prediction models - a literature overview

Reference	Data collection	Derivation/validation	Tested scores/discrimination		Surgery	Population	Follow-up
			Score	AUROC			
Lee et al. (3)	Retro.	Derivation ABCD	ABCD	n.r.	RYGB, MGB	N=63, Asian	12 months
	Prosp.	Validation	ABCD	n.r.	RYGB, MGB	N=176, Asian	12 months
Still et al. (4)	Retro.	Derivation DiaRem	DiaRem	n.r.	RYGB	N=690	≥14 months
	n.r.	Validation cohort 1	DiaRem	n.r.	RYGB	N=276	14 months
	n.r.	Validation cohort 2	DiaRem	n.r.	RYGB	N=113	14 months
Aminian et al. (12)	Retro.	Validation	DiaRem	n.r.	RYGB	N=136, USA	>5 years
Sampaio-Neto et al. (13)	Retro.	Validation	DiaRem	0.841	RYGB	N=70, Brazil	12 months
Cotillard et al. (14)	Prosp.	Validation	DiaRem	n.r.	RYGB	N=84, France	12 months
Wood et al. (15)	Retro.	Validation	DiaRem	n.r.	RYGB	N=407, Non-hispanic white	≥5 years
Lee et al. (16)	Retro.	Validation	DiaRem ABCD	n.r. n.r.	Mixed GBP	N=245, China	12 months
Mehaffey et al. (17)	Prosp.	Validation	DiaRem	n.r.	RYGB	N=31, USA	10 years
Tharakan et al. (18)	Retro.	Validation	DiaRem	n.r.	RYGB	N=262, Ethnically diverse, UK	12 months
Honarmand et al. (8)	Retro.	Validation	DiaRem	0.776*	RYGB	N=900, Canada	12 months
Aron-Wisnewsky et al. (5)	Retro.	Derivation Ad-DiaRem	DiaRem Ad-DiaRem	0.856 0.911	RYGB	N=213, France	12 months
	Retro.	Validation cohort 1	DiaRem Ad-DiaRem	0.893 0.939	RYGB	N=134, France	12 months
	Retro.	Validation cohort 2	DiaRem Ad-DiaRem	0.825 0.882	RYGB	N=99, Israel	12 months
Wood et al. (10)	Retro.	Validation	DiaRem	0.825	RYGB, GB, SG	N=520, White/Hispanic	24 months
Pucci et al. (6)	Retro.	Derivation DiaBetter	DiaRem DiaBetter	0.865 0.867	RYGB, SG	N=210, ≈76% Asian	24 months
		Validation	DiaRem DiaBetter	0.821 0.823	RYGB, SG	N=173, ≈76% Asian	24 months
Ahuja et al. (11)	Retro.	Validation	DiaRem ABCD	0.844 0.769	MGB, OAGB	N=102, India	12 months

Dicker et al. (19)	Retro.	Validation	DiaRem Ad-DiaRem	0.78 0.85	RYGB SG GB	N=1459, Israel	5 years
Kam et al. (20)	Retro.	Validation	ABCD DiaRem Ad-DiaRem DiaBetter	0.750 0.790 0.794 0.804	RYGB	N= 131, Chinese	3 years
Still et al. (21)	Prosp.	Derivation: DiaRem2	DiaRem DiaRem2	0.850 0.876	RYGB	N=307, USA	12 months
Débedat et al. (22)	Prosp.	Derivation: 5y-Ad-DiaRem	DiaRem Ad-DiaRem 5y-Ad-DiaRem	0.81 0.84 0.90	RYGB	N=175, France	5 years
	n.r.	Validation	DiaRem Ad-DiaRem 5y-Ad-DiaRem	0.88 0.89 0.96		N=54, France	5 years
	Prosp.	Validation	5y-Ad-DiaRem	0.85		N=20, Italy	5 years
	n.r.	Validation	5y-Ad-DiaRem	0.92		N=50, Germany	5 years
Aminian et al. (7)	Retro.	Derivation IMS	IMS	n.r.	RYGB, SG	N=659, USA	≥5 years
	Retro.	Validation	IMS	n.r.	RYGB, SG	N=241, USA	≥5 years
Chen et al. (23)	Retro.	Validation	ABCD IMS	n.r.*	RYGB, SAGB, SG	N=310	≥5 years
Shen et al. (24)	Retro.	Validation	DiaRem Ad-DiaRem DiaBetter ABCD IMS	0.804 0.849 0.826 0.824 0.849	SG	N=128, Asian	12 months

IMS, Individualized Metabolic Surgery score; RYGB, Roux-en-Y Gastric Bypass; GBP, gastric bypass; GB, adjustable gastric banding; SG, sleeve gastrectomy; MGB, Mini Gastric Bypass; OAGB, One Anastamosis Gastric Bypass; AUROC, Area Under Receiver Operating Characteristic curve; Retro, retrospective; Prosp., prospective, n.r., not reported. *Analysis limited to complete remission. Table adapted from Zhang et al. (25)

sFigure 1. Patient eligibility and remission/complication rates during follow-up



Full cohort (n=363)

2y remission	220/307 (71.7%) (56 missing)
10y remission	86/249 (34.5%) (114 missing)
Microvascular	67/363 (18.5%) (0 missing)
Macrovascular	109/363 (30.0%) (0 missing)

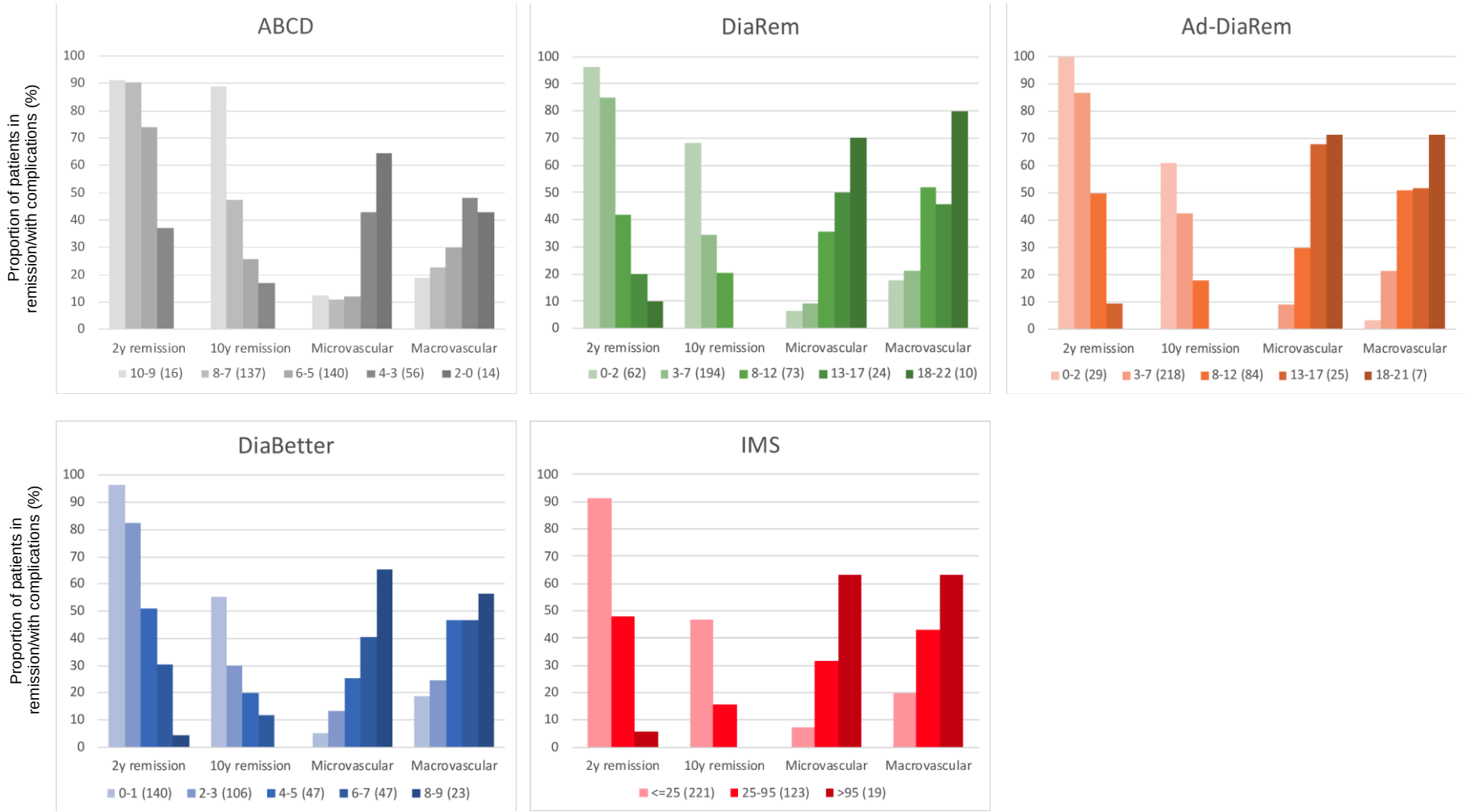
2-year status (n=307)

	Remission n=220	Non-remission n=87	P-value
10y remission	76/167 (45.5%) (53 missing)	4/62 (6.5%) (25 missing)	<0.001
Microvascular	22/220 (10.0%) (0 missing)	36/87 (41.4%) (0 missing)	<0.001
Macrovascular	54/220 (24.5%) (0 missing)	39/87 (44.8%) (0 missing)	<0.001

10-year status (n=249)

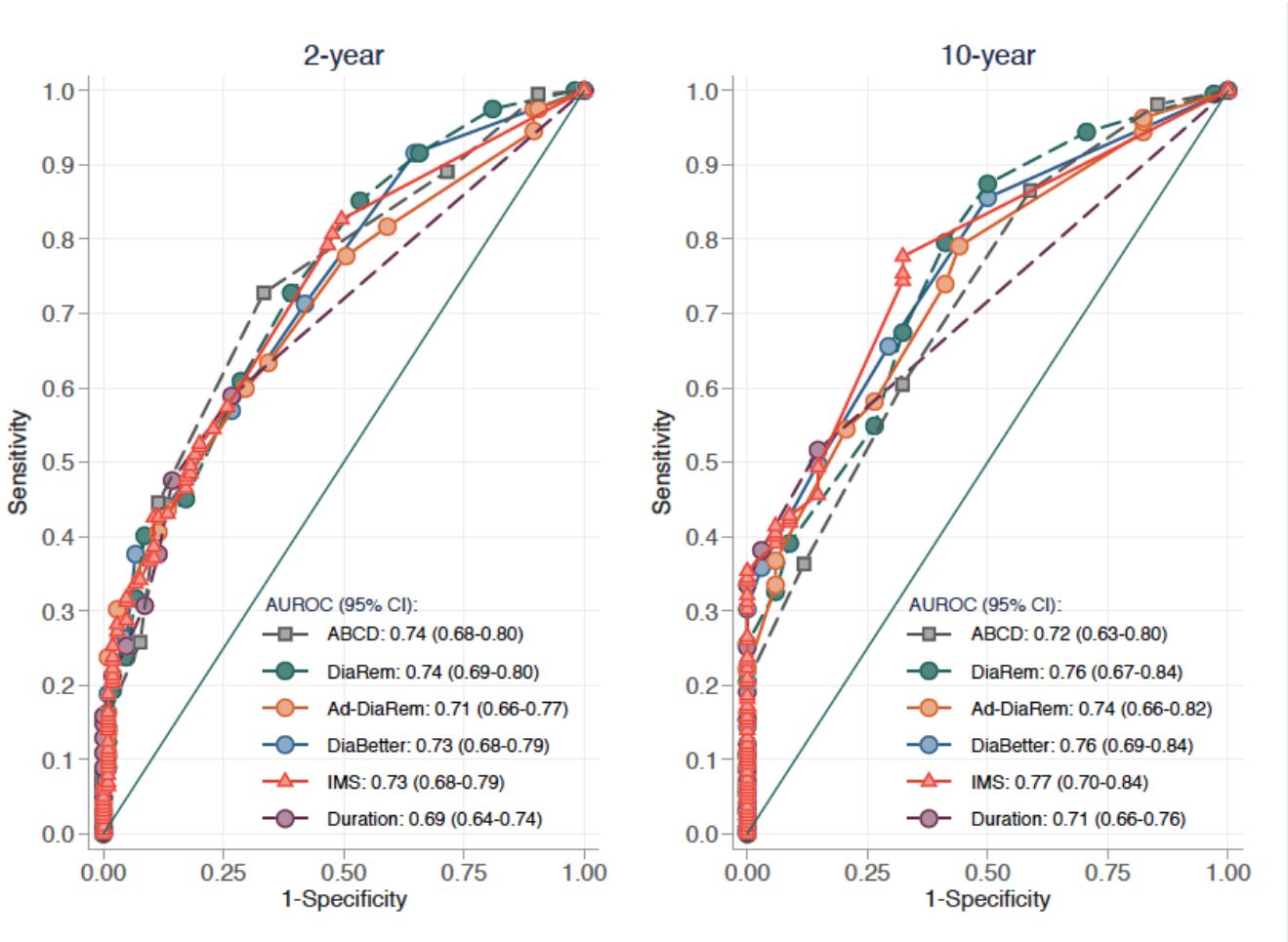
	Remission n=86	Non-remission n=163	P-value
2y remission	76/80 (95.0%) (6 missing)	91/149 (61.1%) (14 missing)	<0.001
Microvascular	2/86 (2.3%) (0 missing)	50/163 (30.7%) (0 missing)	<0.001
Macrovascular	9/86 (10.5%) (0 missing)	67/163 (41.1%) (0 missing)	<0.001

sFigure 2. Illustration of diabetes remission rate (2 and 10 years), and micro- and macrovascular complication rate (over 15 years) by previously proposed score groups using data from the SOS study.



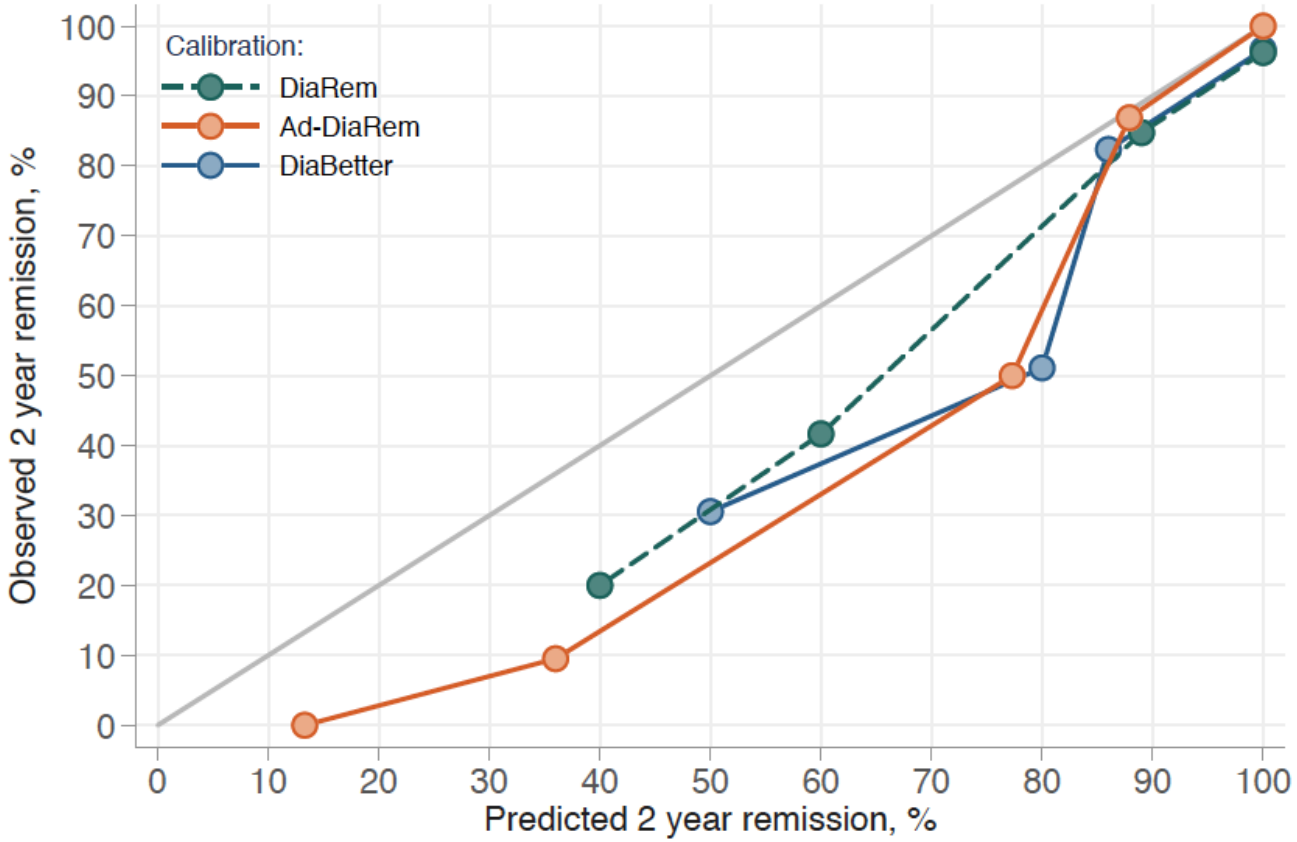
Bar colors indicate score groups: The number of individuals with register data on microvascular/microvascular complications are indicated in parenthesis (note that for some patients, information on remission status at 2 or 10 years was not available (missing values are reported in sFigure 1)).

sFigure 3. Comparison of the diagnostic value of the ABCD (grey squares), DiaRem (green circles), DiaBetter (blue circles), Ad-DiaRem (orange circles), and IMS (red triangles) scores, and diabetes duration (purple circles) for *complete* diabetes remission in the SOS surgery group after 2 years (panel A) and 10 years (panel B) of follow-up.



Nonparametric receiver operating characteristic curves (AUROCs) were used to test the accuracy of the prediction models. The closer the area under the curve is to a value of 1, the more accurate the model. Sensitivity is shown on the y-axis and specificity on the x-axis. The diagonal line (reference) is the line of no discrimination; it divides the ROC space into two, the points above the diagonal represent classification results better than random.

sFigure 4. Calibration plot depicting predicted chance of type 2 diabetes remission (DiaRem (6), Ad-DiaRem (19) and DiaBetter (6)) against observed type 2 diabetes remission (SOS surgery group) 2 years after bariatric surgery.



Categories of scores:
DiaBetter: 0-1, 2-3, 4-5 and 6-7. DiaRem: 0-2, 3-7, 8-12, 13-17. Ad-DiaRem: 0-2, 3-7, 8-12, 13-17
Chi2 goodness-of-fit: DiaBetter p<0.001; DiaRem p<0.001; Ad-DiaRem p<0.001

The solid line (45°) from zero denotes ideal calibration (slope=1, intercept=0) and the other lines are calibration curves for each score. Note that the highest score groups (DiaRem 18-21, Ad-DiaRem 18-22, DiaBetter 8-9) were excluded due to low numbers of events.

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