Diabetes and Stroke

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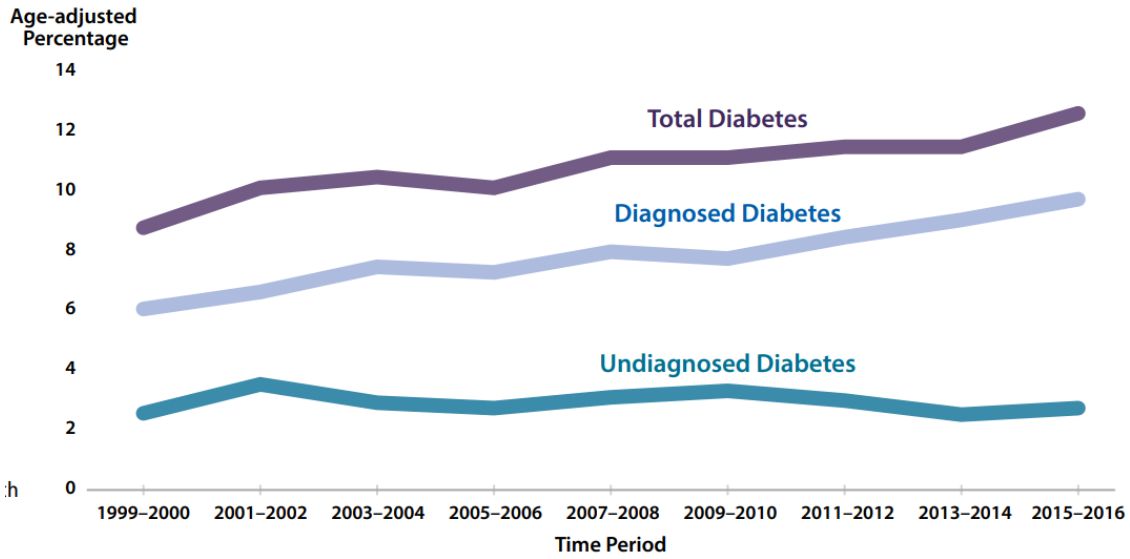
Objectives

1. Epidemiology
2. (Ischemic) Stroke Mechanisms
3. Poststroke Hyperglycemia
4. Secondary (Ischemic) Stroke Prevention

Epidemiology – Diabetes & Stroke



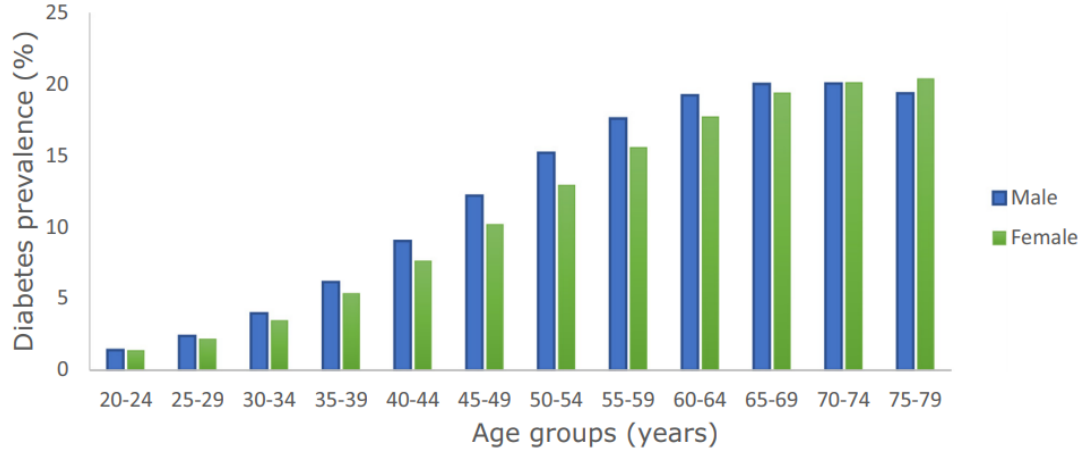


Fig. 1 – Diabetes prevalence by age and sex in 2019.

Diabetes Res Clin Pract. 2019;157:107843.
Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020.

Diabetes Increases Ischemic Stroke Risk ~2-Fold

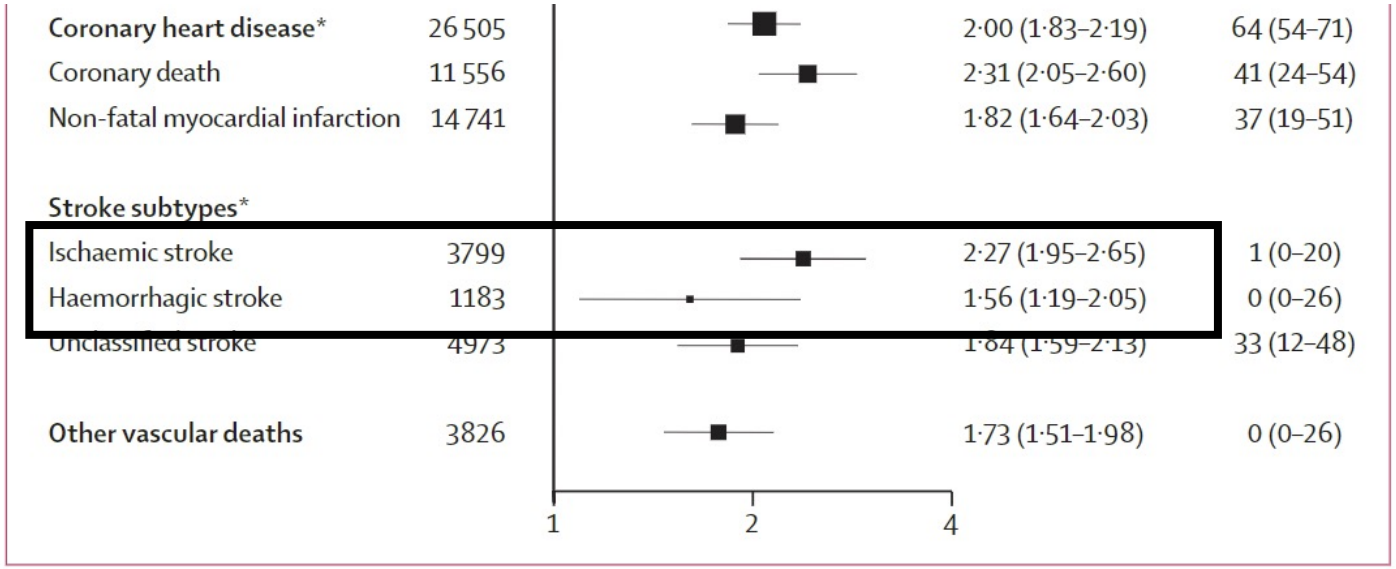


Figure 1: **Hazard ratios (HRs) for vascular outcomes in people with versus those without diabetes at baseline**
Analyses were based on 530 083 participants. HRs were adjusted for age, smoking status, body-mass index, and systolic blood pressure, and, where appropriate, stratified by sex and trial arm. 208 coronary heart disease outcomes that contributed to the grand total could not contribute to the subtotals of coronary death or non-fatal myocardial infarction because there were fewer than 11 cases of these coronary disease subtypes in some studies. *Includes both fatal and non-fatal events.

Lancet. 2010;375(9733):2215-2222.
Diabetologia. 2001;44 Suppl 2:S54-S64.
Diabetes Care. 2007;30(7):1730-1735.

Diabetes & Intracerebral Hemorrhage

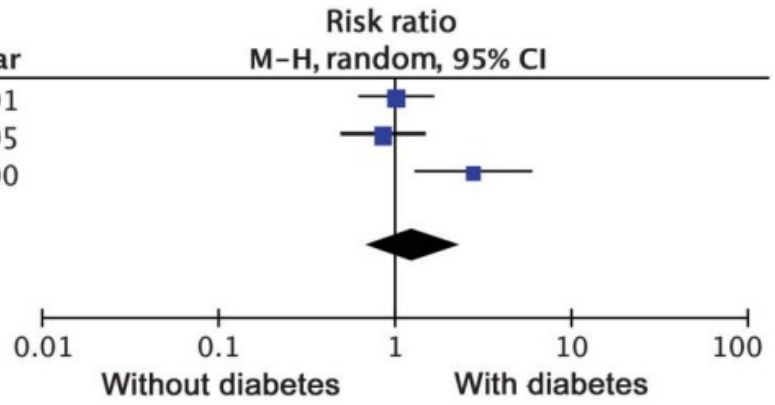
- ICH Occurrence
  - Case-control studies → Modest association: odds ratio 1.23 (95% CI: 1.04 – 1.45)

Figure 2 **Association between diabetes mellitus and the incidence of intracerebral hemorrhage (ICH) in 3 cohort studies, ordered by study mid-year**

	With diabetes		Without diabetes				
Study or subgroup	Events	Total	Events	Total	Weight	Risk ratio M–H, random, 95% CI	Year
Ref 13	18	2872	116	18808	37.1%	1.02 (0.62, 1.67)	1991
Ref 28	13	2035	251	33622	35.0%	0.86 (0.49, 1.49)	1995
Ref 32	7	817	81	26272	27.9%	2.78 (1.29, 6.00)	2000
Total (95% CI)		**5724**		**78702**	**100.0%**	**1.27 (0.68, 2.36)**	
Total events	38		448				

Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 6.54$, df = 2 ($p = 0.04$); $I^2 = 69\%$

Test for overall effect: $Z = 0.74$ ($p = 0.46$)



Neurology. 2016;87(9):870-878.

Stroke Risk Higher in Women with Diabetes

Sex differences:

- vascular risk factor control
- progression of atherosclerosis
- novel risk factors

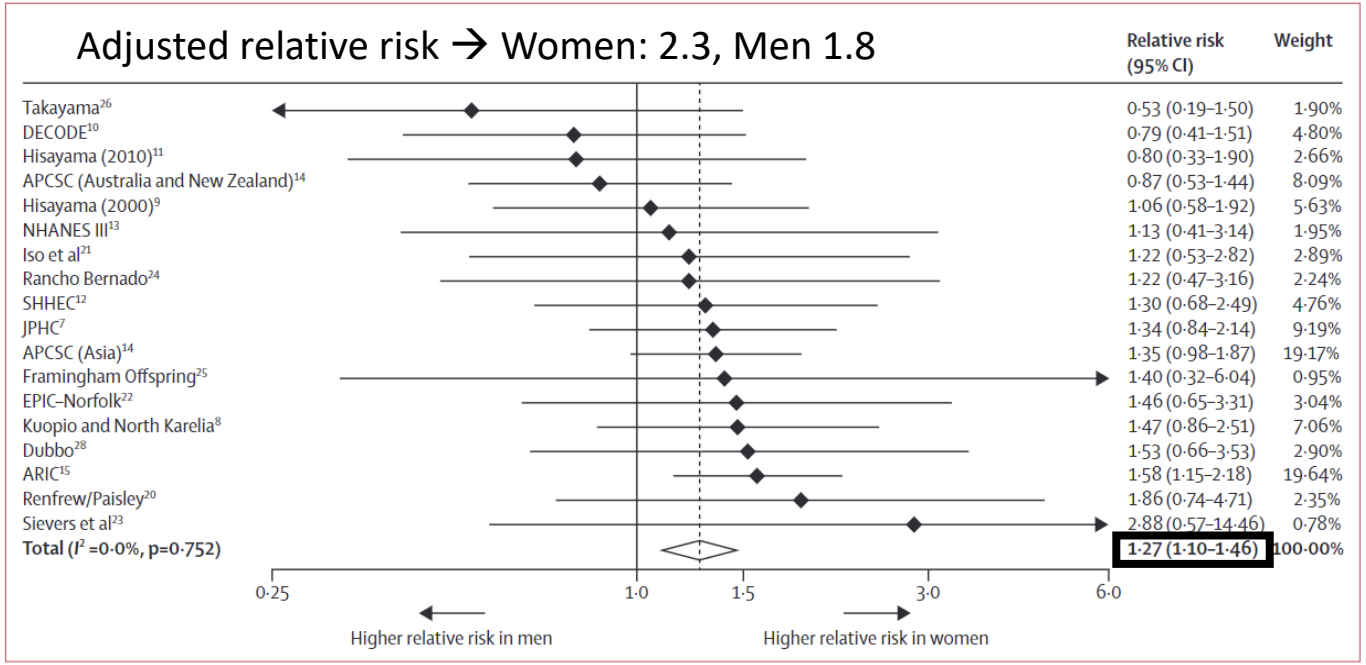


Figure 3: Maximum-adjusted women-to-men ratio of relative risks for any stroke, comparing individuals with diabetes to those without diabetes

Lancet. 2014;383(9933):1973-1980.

Diabetes Duration Increases Ischemic Stroke Risk

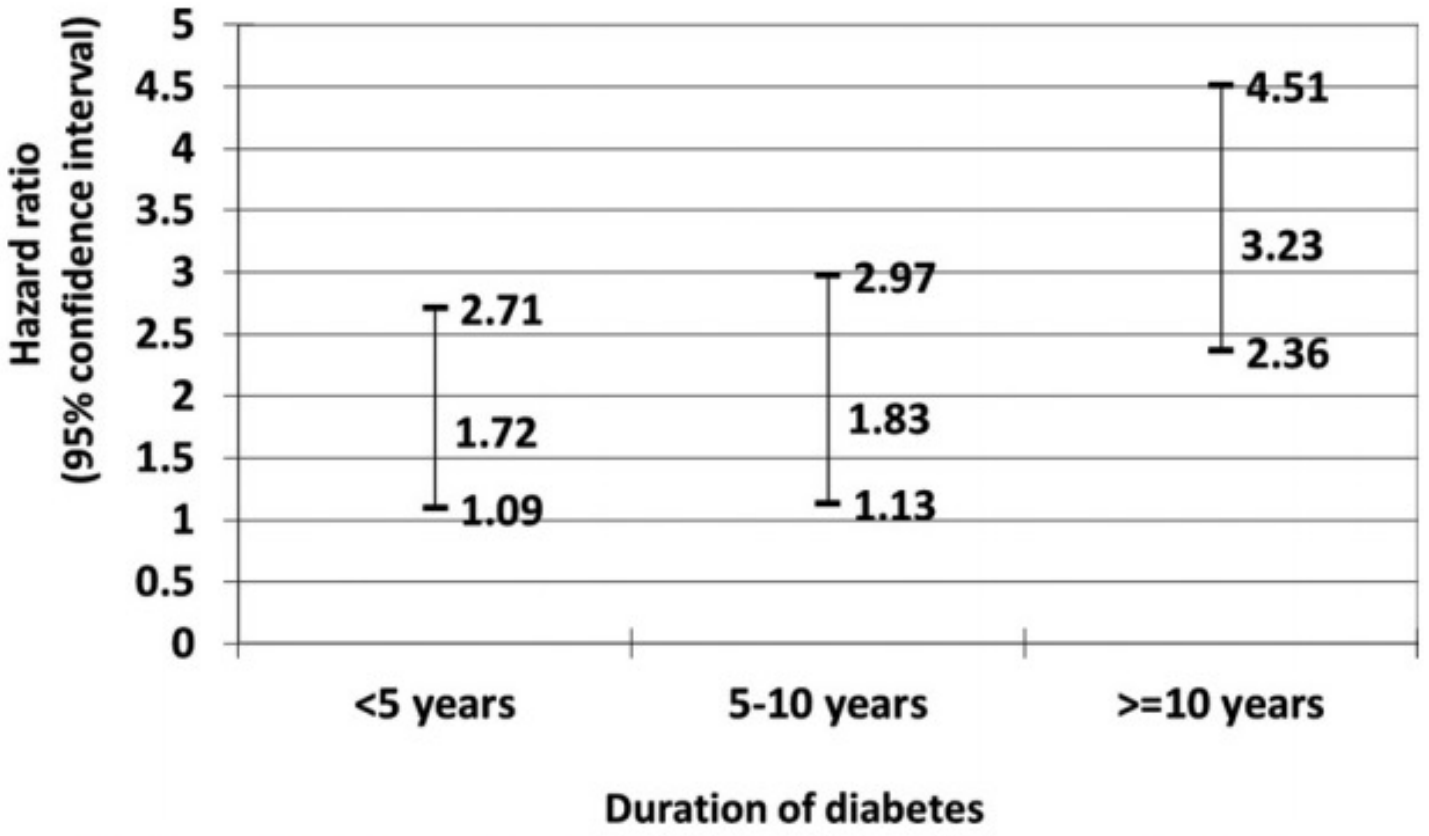


Figure. Risk of ischemic stroke and duration of diabetes.

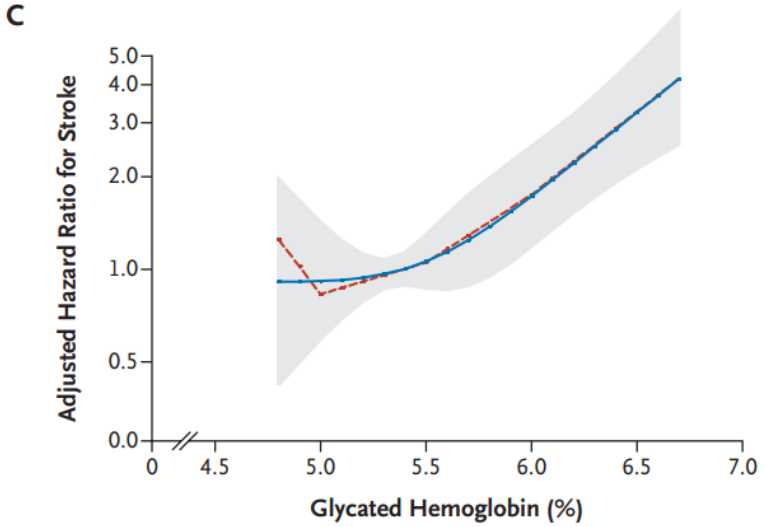
Stroke. 2012;43(5):1212-1217.
J Am Coll Cardiol. 2016;67(3):239-247.
Diabetes Care. 2007;30(7):1730-1735.

Prediabetes & Insulin Resistance (Nondiabetics) Increases Stroke Risk

N Engl J Med. 2010;362(9):800-811.
BMJ. 2012;344:e3564.
Arch Neurol. 2010;67(10):1195-1200.
Stroke. 2011;42(12):3347-3351.

Table 2. Adjusted Hazard Ratios for Selected Clinical Outcomes in the Study Population during the 15-Year Study Period, According to the Glycated Hemoglobin Category at Baseline and the Model.*

Outcome	Model 1a	Model 2a	Model 3a
Ischemic stroke			
Glycated hemoglobin category — hazard ratio (95% CI)			
<5.0%	1.06 (0.65–1.71)	1.09 (0.67–1.76)	1.09 (0.68–1.77)
5.0 to <5.5% (reference)	1.00	1.00	1.00
5.5 to <6.0%	1.27 (0.97–1.67)	1.17 (0.89–1.53)	1.16 (0.89–1.53)
6.0 to <6.5%	2.63 (1.92–3.61)	2.22 (1.60–3.08)	2.19 (1.58–3.05)
≥6.5%	3.68 (2.56–5.30)	3.16 (2.15–4.64)	2.96 (1.87–4.67)
P value for trend	<0.001	<0.001	<0.001
Glycated hemoglobin value — hazard ratio (95% CI)	1.41 (1.30–1.54)	1.34 (1.22–1.48)	1.55 (1.28–1.88)
C statistic	0.7229	0.7581	0.7594



Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) Index =

$$\frac{Fasting\ Blood\ Glucose \cdot Fasting\ Insulin}{22.5}$$

- HOMA-IR<1 → insulin sensitive
- HOMR-IR>3 → significant insulin resistance

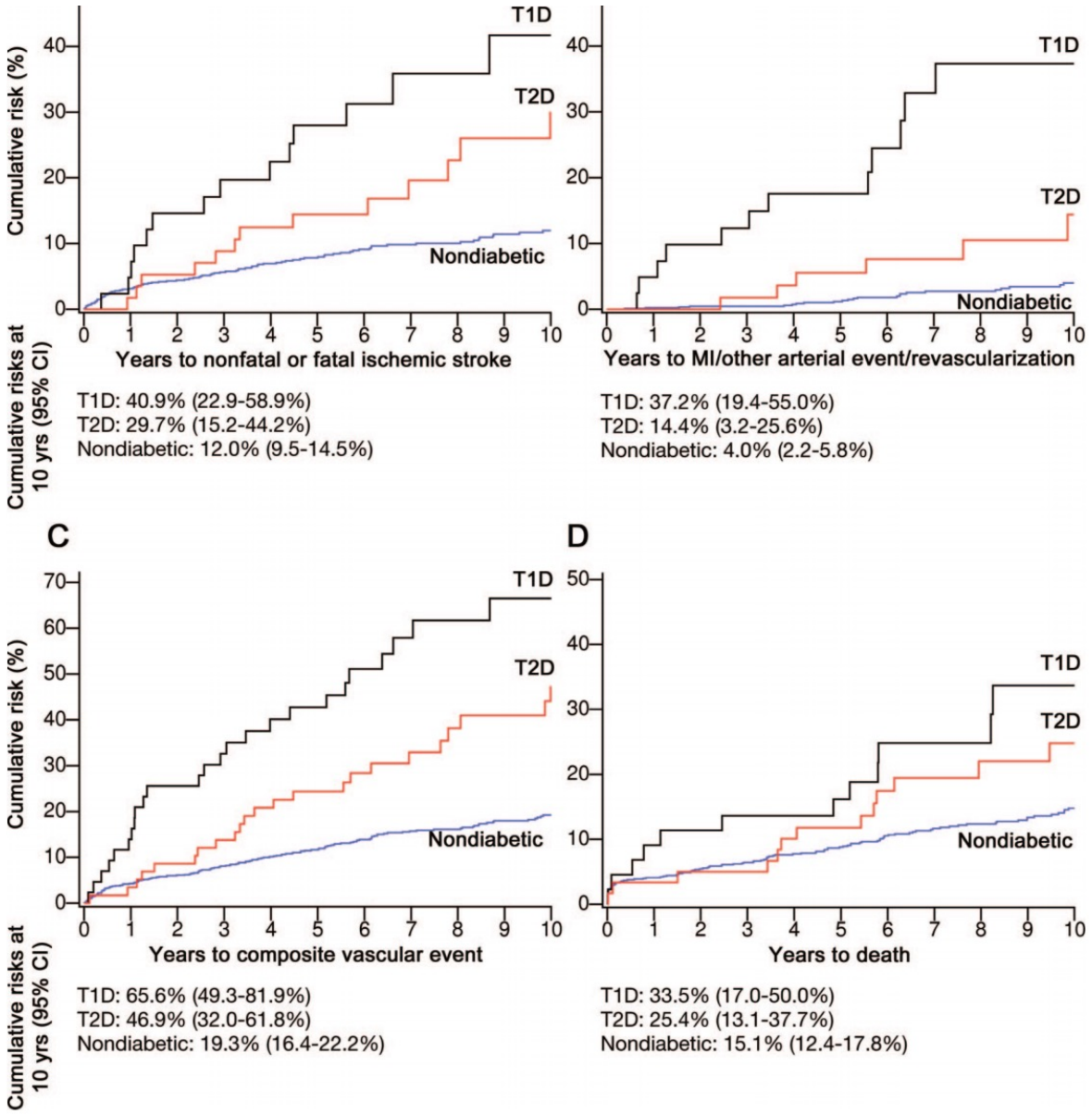
Table 3. Relation Between HOMA-IR Quartiles and Risk of Ischemic Stroke, Myocardial Infarction, Vascular Death, and Combined Vascular Events

	Hazard Ratio (95% CI)			
Adjusted for	Model 1: Age	Model 2: Sociodemographics[a]	Model 3: Sociodemographics and Metabolic Syndrome	Model 4: Multivariate Adjusted[b]
Ischemic stroke				
HOMA	Trend $P = .04$	Trend $P = .06$	Trend $P = .07$	Trend $P = .08$
Q1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Q2	1.88 (0.72-4.87)	1.87 (0.71-4.89)	1.87 (0.71-4.91)	1.59 (0.58-4.33)
Q3	0.93 (0.29-2.95)	0.87 (0.27-2.81)	0.88 (0.27-2.86)	0.65 (0.18-2.36)
Q4	3.11 (1.25-7.76)	2.98 (1.16-7.62)	3.01 (1.13-8.04)	2.97 (1.05-8.35)
HOMA Q4 vs Q1-Q3	2.47 (1.28-4.77)	2.40 (1.23-4.67)	2.43 (1.21-4.91)	2.83 (1.34-5.99)
Myocardial infarction				
HOMA Q4 vs Q1-Q3	1.87 (1.00-3.48)	1.79 (0.94-3.39)	1.48 (0.76-2.88)	1.77 (0.88-3.58)
Vascular death				
HOMA Q4 vs Q1-Q3	1.27 (0.84-1.93)	1.34 (0.87-2.05)	1.25 (0.80-1.96)	1.10 (0.69-1.74)
Combined vascular events				
HOMA Q4 vs Q1-Q3	1.45 (1.04-2.03)	1.52 (1.08-2.14)	1.37 (0.96-1.96)	1.25 (0.86-1.82)

Diabetes & Stroke Outcomes

- Stroke recurrence
- Vascular events or death
- Post-stroke dementia
- Functional disability

Lancet Neurol. 2009;8(11):1006-1018.
Neurology. 2011;76(21):1831-1837.
J Stroke Cerebrovasc Dis. 2015;24(9):1961-1968.
Neurology. 2016;87(9):870-878.
J Diabetes Investig. 2019;10(3):780-792.

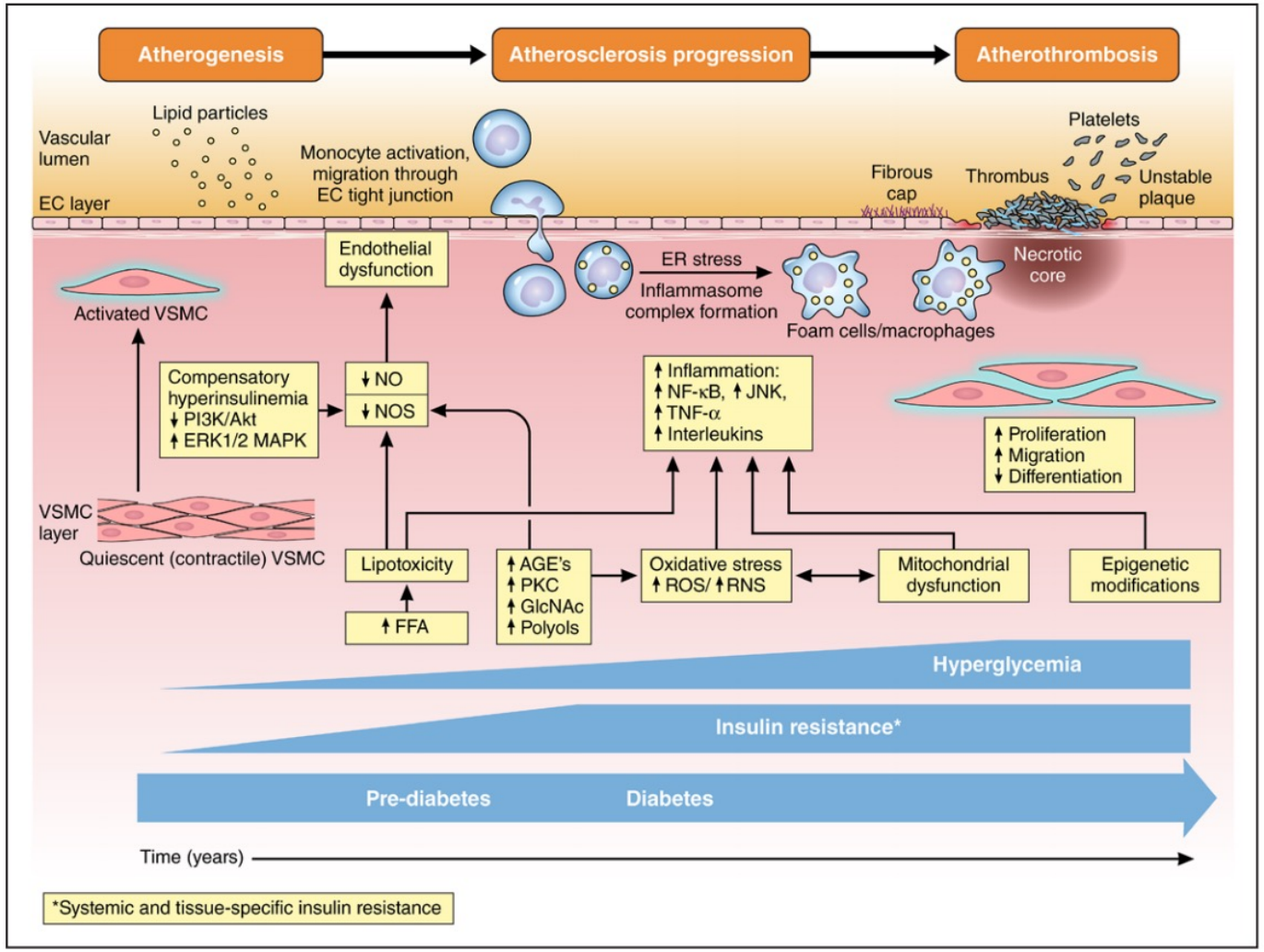


Pathophysiology

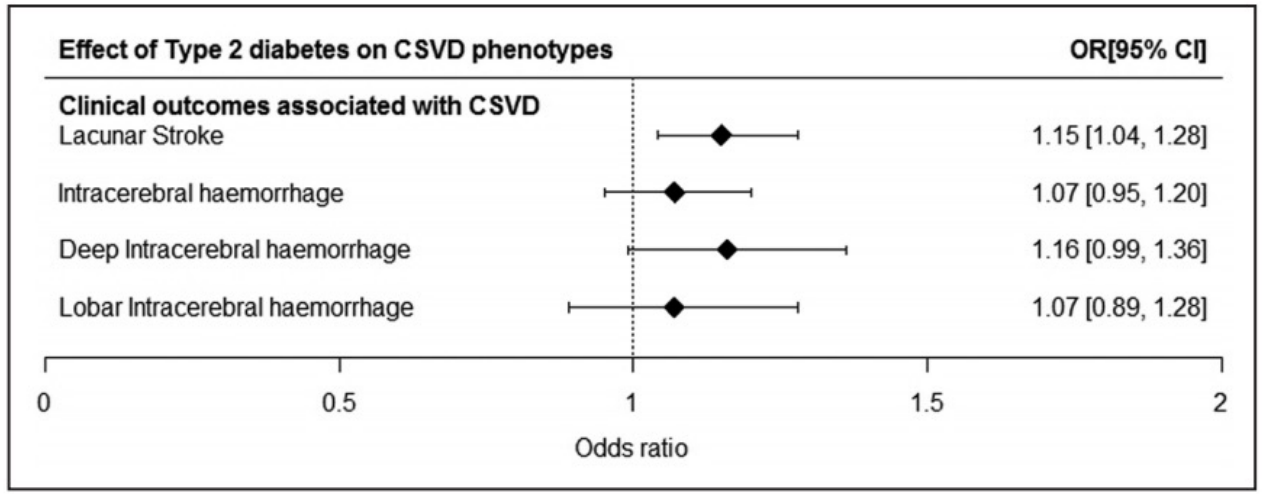
- Stroke mechanisms
  - Atherosclerosis
  - Lacunar
  - Cardiac

- Insulin resistance + hyperinsulinemia + hyperglycemia

→ Atherosclerosis



Stroke. 2011;42(9):2611-2614.
Circulation. 2016;133(24):2459-2502.



- Mendelian randomization study → support a causal association with lacunar infarction

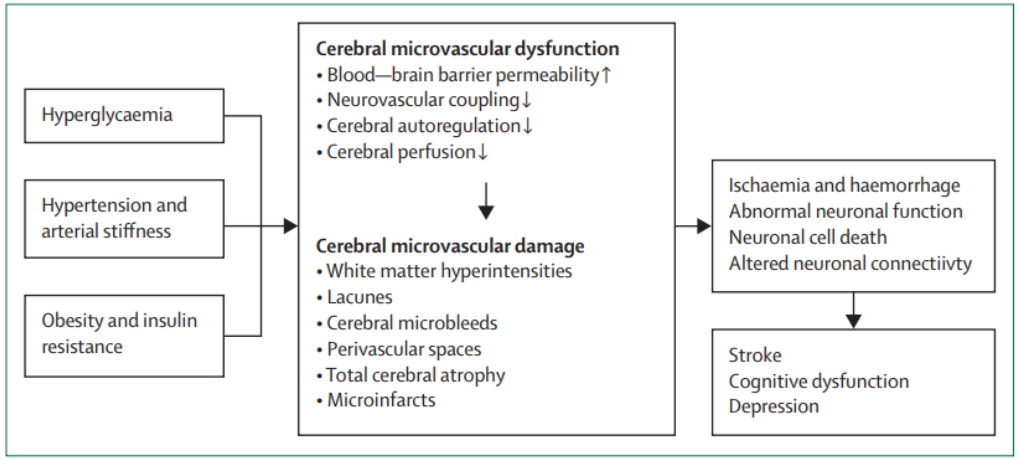


Figure 2: **Presumed pathway by which type 2 diabetes-related cerebral microvascular dysfunction contributes to stroke, cognitive dysfunction, and depression**

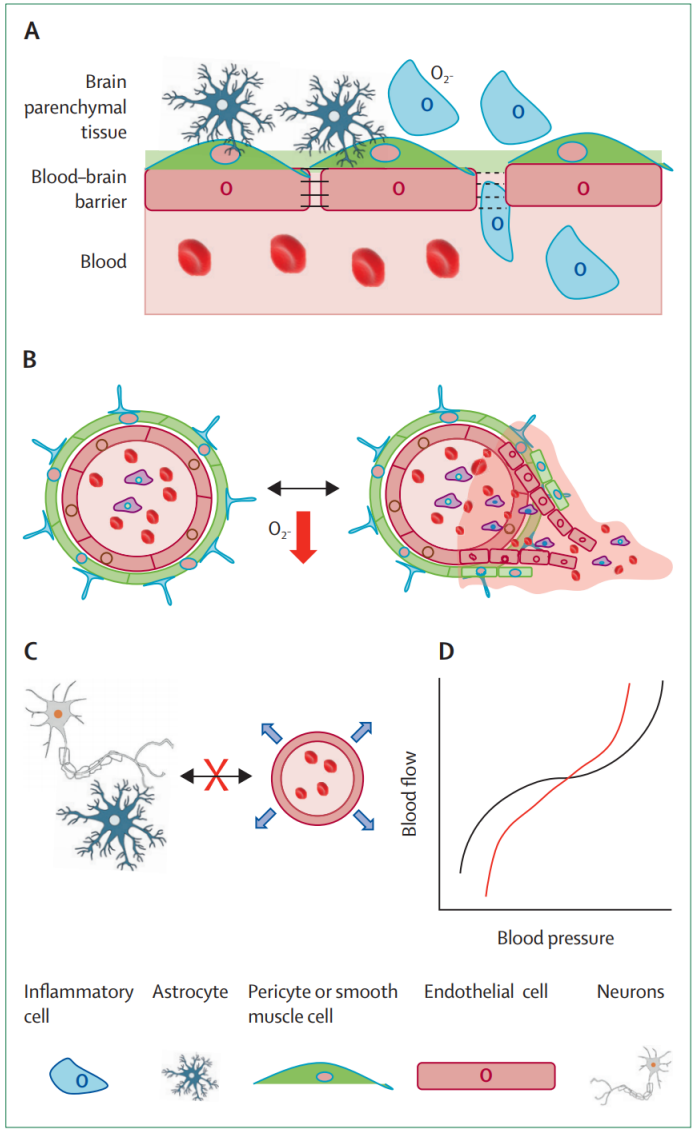


Figure 1: **Detrimental effects of cerebral microvascular dysfunction**

Neurology. 2004;62(9):1558-1562.
Nutr Metab Cardiovasc Dis. 2008;18(2):152-157.
Stroke. 2018;49(6):1325-1331.
Lancet Diabetes Endocrinol. 2020;8(4):325-336.

- Cardiomyopathy
  - CAD/MI
  - Non-ischemic cardiomyopathy
- Increases atrial fibrillation risk (~40%)
  - Increased AF-related stroke risk

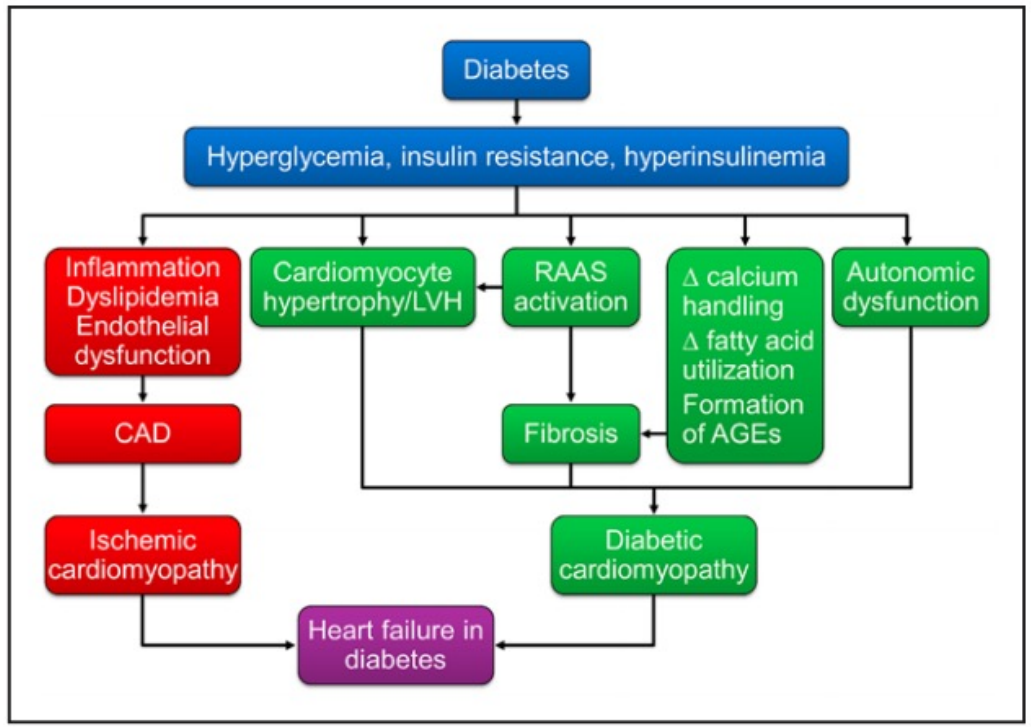


Figure 1. Pathophysiology of heart failure in diabetes mellitus.

	Score
$CHADS_2$ acronym	
Congestive heart failure	1
Hypertension	1
Aged ≥75 years	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6
CHA_2DS_2-VASc acronym	
Congestive heart failure/LV dysfunction	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (previous MI, PAD, or aortic plaque)	1
Aged 65–74 years	1
Sex category (ie, female sex)	1
Maximum score	9

TIA=transient ischaemic attack. TE=thromboembolic. LV=left ventricular. MI=myocardial infarction. PAD=peripheral artery disease.

Table 1: Definition and scores for $CHADS_2$ and CHA_2DS_2-VASc

	Adjusted stroke rate (% per year)
$CHADS_2$ score*	
0	1·9%
1	2·8%
2	4·0%
3	5·9%
4	8·5%
5	12·5%
6	18·2%
CHA_2DS_2-VASc score†	
0	0%
1	1·3%
2	2·2%
3	3·2%
4	4·0%
5	6·7%
6	9·8%
7	9·6%
8	6·7%
9	15·2%

*Adjusted stroke rate scores based on data from Gage and colleagues.[46] These stroke rates are based on data for hospitalised patients with atrial fibrillation and published in 2001. Because stroke rates are decreasing, actual rates of stroke in contemporary non-hospitalised cohorts might vary from these estimates.
†Adjusted stroke rate scores based on data from Lip and colleagues.[50] Actual rates of stroke in contemporary cohorts might vary from these estimates.

Table 2: Stroke risk stratification with the $CHADS_2$ and CHA_2DS_2-VASc scores

Am J Cardiol. 2011;108(1):56-62.
Lancet. 2012;379(9816):648-661.
Circulation. 2019;140(7):e294-e324.

Poststroke Hyperglycemia

- Acute Ischemic stroke: ~40%
  - Diabetics: 80%
  - Non-diabetics: 30-50%
- Unrecognized diabetes
- “Stress Hyperglycemia”

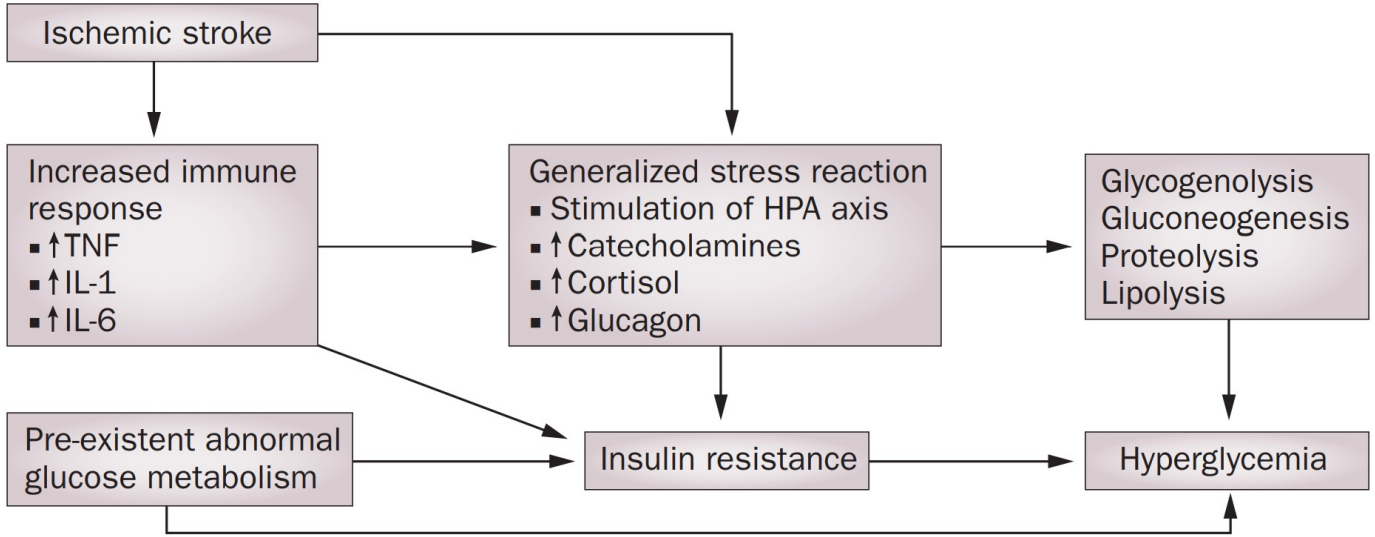


Figure 1 | Mechanisms leading to hyperglycemia in patients with ischemic stroke.

Neurology. 2002 Jul 9;59(1):67-71.
Diabetes Care. 2006;29(8):1839-1844.
Nat Rev Neurol. 2010;6(3):145-155.

Hyperglycemia and Stroke Outcomes

- Short-term mortality
- Poor functional outcomes

- Increased infarct size & growth
- Poststroke infection
- Reduced recanalization (IV-tPA)
- Hemorrhagic transformation

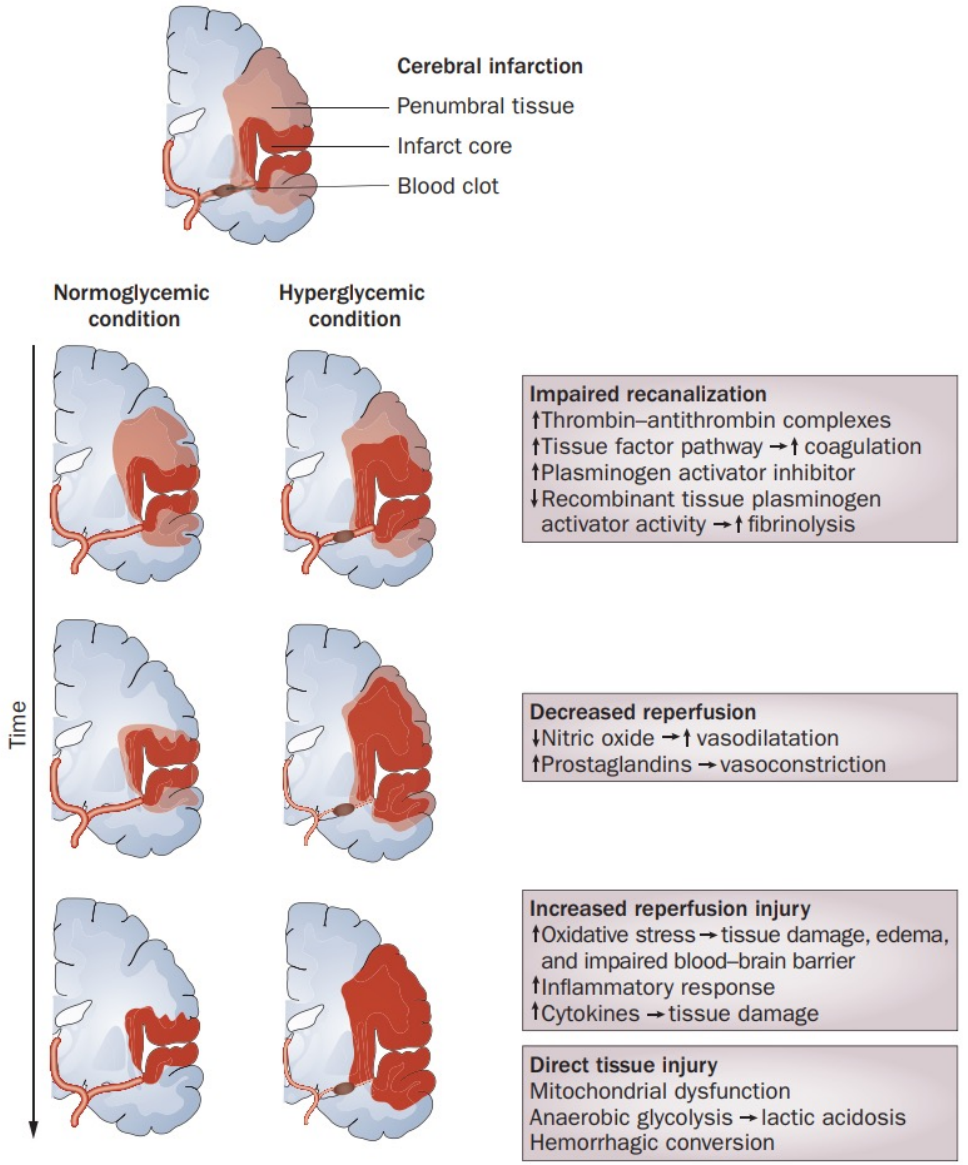


Figure 2 | Schematic representation of infarct evolution over time. Hyperglycemia can have deleterious effects on various physiological processes associated with infarct evolution in patients with acute ischemic stroke.

Stroke. 2001;32(10):2426-2432.
Stroke. 2005;36(8):1705-1709.
Cerebrovasc Dis. 2009;28(2):119-123.
Nat Rev Neurol. 2010;6(3):145-155.
Stroke. 2012;43(1):243-245.
Stroke. 2012;43(11):2904-2909.
Neurology. 2017;88(15):1415-1421.

JAMA | Original Investigation

Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke

The SHINE Randomized Clinical Trial

- Acute Ischemic Stroke + Hyperglycemia:
  - BG > 110 mg/dL (diabetics)
  - BG ≥ 150 mg/dL (non-diabetics)
- ≤ 12 hours of stroke onset

- Intensive: BG 80-130 mg/dL (IV insulin)
- Standard: BG 80-179 mg/dL (subq SSI)

* Treatment period = 72 hours

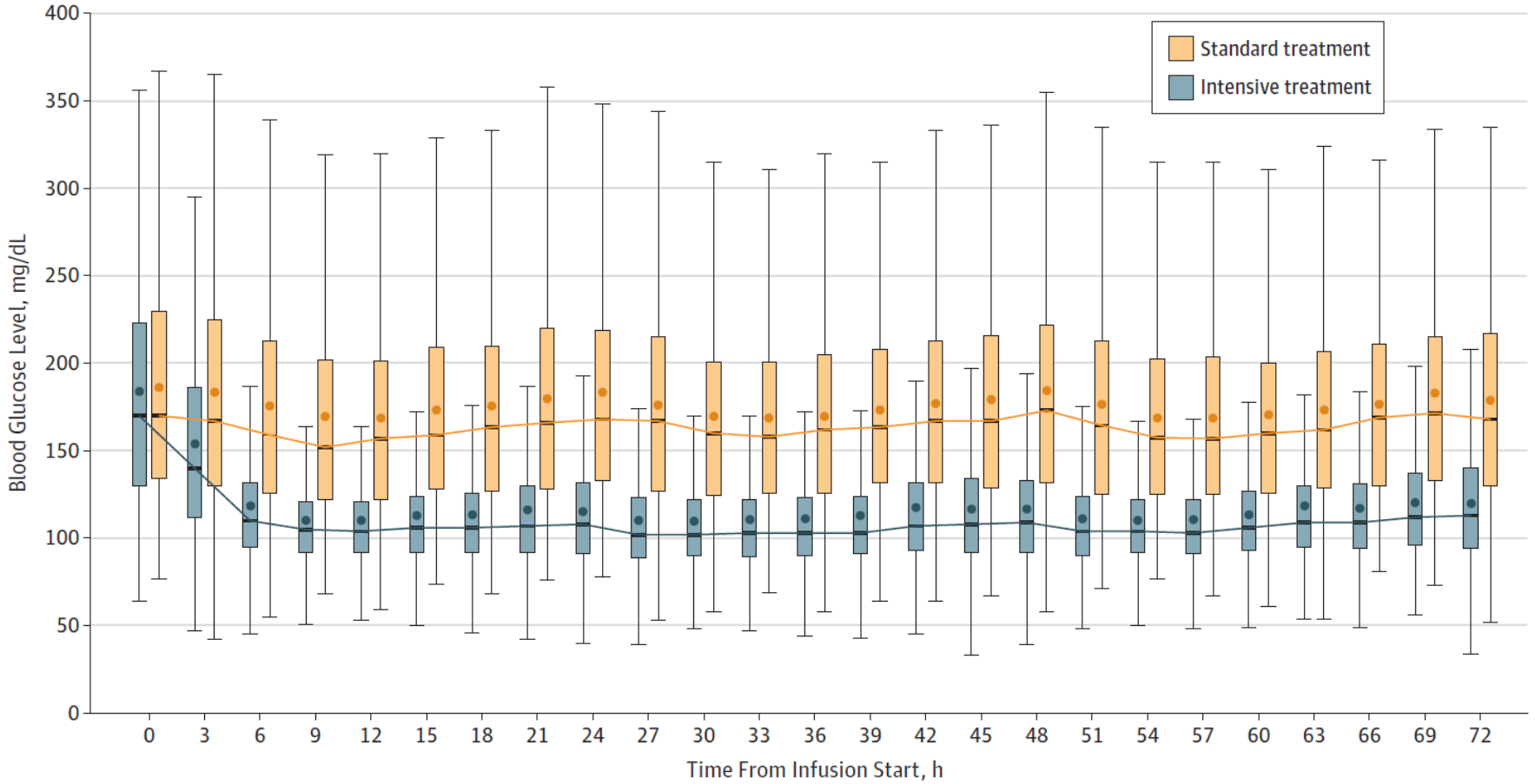
- Outcomes: % favorable outcome (mRS dependent on baseline NIHSS), severe hypoglycemia (glucose <40 mg/dL)

JAMA. 2019;322(4):326-335.

Table 1. Baseline Patient Characteristics

Characteristic	Treatment of Hyperglycemia	
	Intensive (n = 581)	Standard (n = 570)
Age, median (IQR), y	66 (57-75)	66 (57-76)
Sex, No. (%)		
Male	321 (55.3)	306 (53.7)
Female	260 (44.8)	264 (46.3)
Race, No./total No. (%)		
White	366/560 (65.4)	368/547 (67.3)
Black	180/560 (32.1)	154/547 (28.2)
Asian	12/560 (2.1)	18/547 (3.3)
Other[a]	2/560 (0.4)	7/547 (1.3)
Hispanic ethnicity, No./total No. (%)	87/547 (15.9)	91/540 (16.9)
Final diagnosis, No. (%)		
Ischemic stroke	542 (93.3)	524 (91.9)
Transient ischemic attack	8 (1.4)	12 (2.1)
Other[b]	31 (5.3)	34 (6.0)
Use of reperfusion therapies, No. (%)[c]		
Intravenous tissue plasminogen activator	372 (64.0)	353 (61.9)
Mechanical thrombectomy	74 (12.7)	72 (12.6)
Intra-arterial drug therapy	14 (2.4)	21 (3.7)
Medical history, No. (%)		
Hypertension	513 (88.3)	502 (88.1)
Type 2 diabetes	468 (80.6)	455 (79.8)
Hyperlipidemia	350 (60.2)	327 (57.4)
Coronary artery disease	159 (27.4)	167 (29.3)
Atrial fibrillation	124 (21.3)	106 (18.6)
Previous ischemic stroke	104 (17.9)	99 (17.4)
Previous large vessel atherosclerosis	42 (7.2)	39 (6.8)
Blood glucose level, median (IQR), mg/dL	188 (153-250)	187 (155-248)
NIHSS score, median (IQR)[d]	7 (5-12)	7 (5-13)
Stroke category, No. (%)		
Mild (NIHSS score of 3-7)	291 (50.1)	291 (51.1)
Moderate (NIHSS score of 8-14)	177 (30.5)	158 (27.7)
Severe (NIHSS score of 15-22)	113 (19.4)	121 (21.2)

Figure 2. Blood Glucose Concentrations in 3-Hour Intervals During the Treatment Period by Treatment Group



Intensive treatment																									
No. of patients	577	573	570	564	562	556	544	534	526	508	495	479	467	464	442	423	397	384	374	366	346	339	328	310	263
No. of glucose values	577	1481	1690	1480	1403	1323	1287	1335	1353	1337	1290	1236	1179	1151	1110	1053	1044	1034	1012	938	863	835	824	765	524
Standard treatment																									
No. of patients	565	558	552	539	541	530	524	511	499	490	494	486	480	470	460	447	432	423	401	388	394	381	377	361	278
No. of glucose values	565	1363	1039	598	596	577	562	558	559	525	528	523	518	510	496	470	486	454	428	417	421	401	398	392	362

JAMA. 2019;322(4):326-335.

Table 2. Primary Outcome, Secondary Outcomes, and Adverse Events

	Treatment of Hyperglycemia		Unadjusted Risk Difference (95% CI), %	Relative Risk (95% CI)		P Value
	Intensive (n = 581)	Standard (n = 570)		Unadjusted	Adjusted[a]	
Primary Outcome						
Favorable 90-d modified Rankin Scale score, No. (%)[b]	119 (20.5)	123 (21.6)	−0.83 (−5.72 to 4.06)	0.96 (0.77 to 1.20)	0.97 (0.87 to 1.08)	.55[c]
Secondary Outcomes[d]						
Favorable 90-d NIHSS score, No./total No. (%)[e]	152/348 (43.7)	166/371 (44.7)	−1.07 (−8.33 to 6.20)	0.98 (0.83 to 1.15)	1.00 (0.93 to 1.08)	.77[f]
Favorable 90-d Barthel Index score, No./total No. (%)[g]	271/491 (55.2)	261/477 (54.7)	0.48 (−5.79 to 6.75)	1.01 (0.90 to 1.13)	1.00 (0.95 to 1.05)	.88[f]
90-d Stroke Specific Quality of Life score[h]						
No. of patients	442	432				
Median (IQR)	3.75 (2.98 to 4.40)	3.69 (3.02 to 4.46)	0.06 (−0.13 to 0.25)			.74[i]
Adverse Events						
Severe hypoglycemia (glucose level <40 mg/dL), No. (%)	15 (2.6)	0	2.58 (1.29 to 3.87)			<.001[j]
Death, No. (%)	54 (9.3)	65 (11.4)	−2.11 (−5.63 to 1.41)	0.82 (0.58 to 1.15)		.24[f]

Modified Rankin Scale	
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Cochrane Database of Systematic Reviews

Insulin for glycaemic control in acute ischaemic stroke

Cochrane Systematic Review - **Intervention** | Version published: 23 January 2014 see what's new

https://doi.org/10.1002/14651858.CD005346.pub4

JAMA. 2019;322(4):326-335.
Cochrane Database Syst Rev. 2014;(1):CD005346.

Secondary (Ischemic) Stroke Prevention

- Ischemic Stroke / TIA → HgA1c or fasting blood glucose
- Target HgA1c <7%
  - <6.5% (younger)
    - Hypoglycemia
  - Individualize

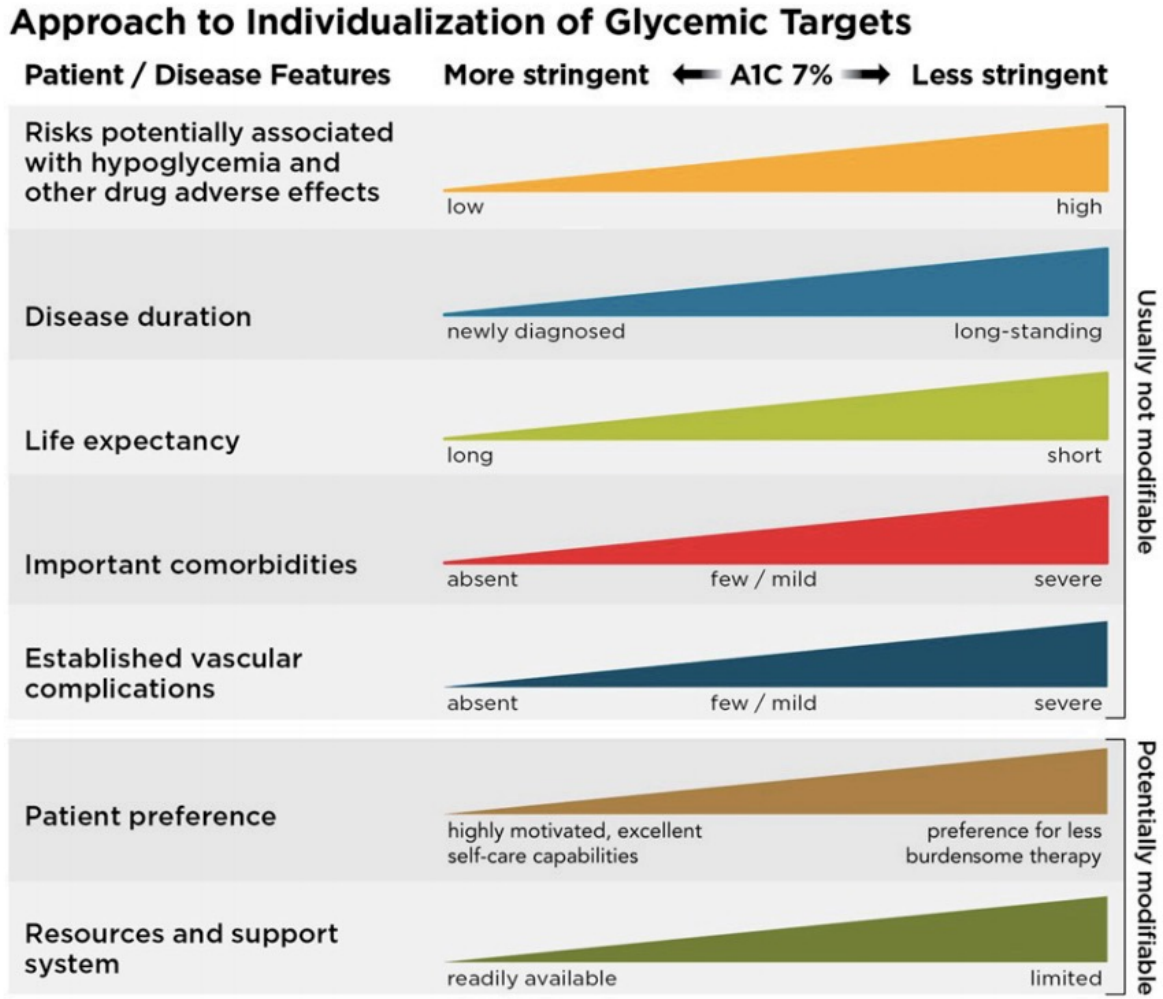


Figure 6.2—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (47).

Stroke. 2014;45(7):2160-2236.
Diabetes Care. 2020 Jan;43(Suppl 1):S66-S76.

Glycemic Control & Stroke Prevention

Avg HgA1c = 6.6%

Avg HgA1c = 7.5%

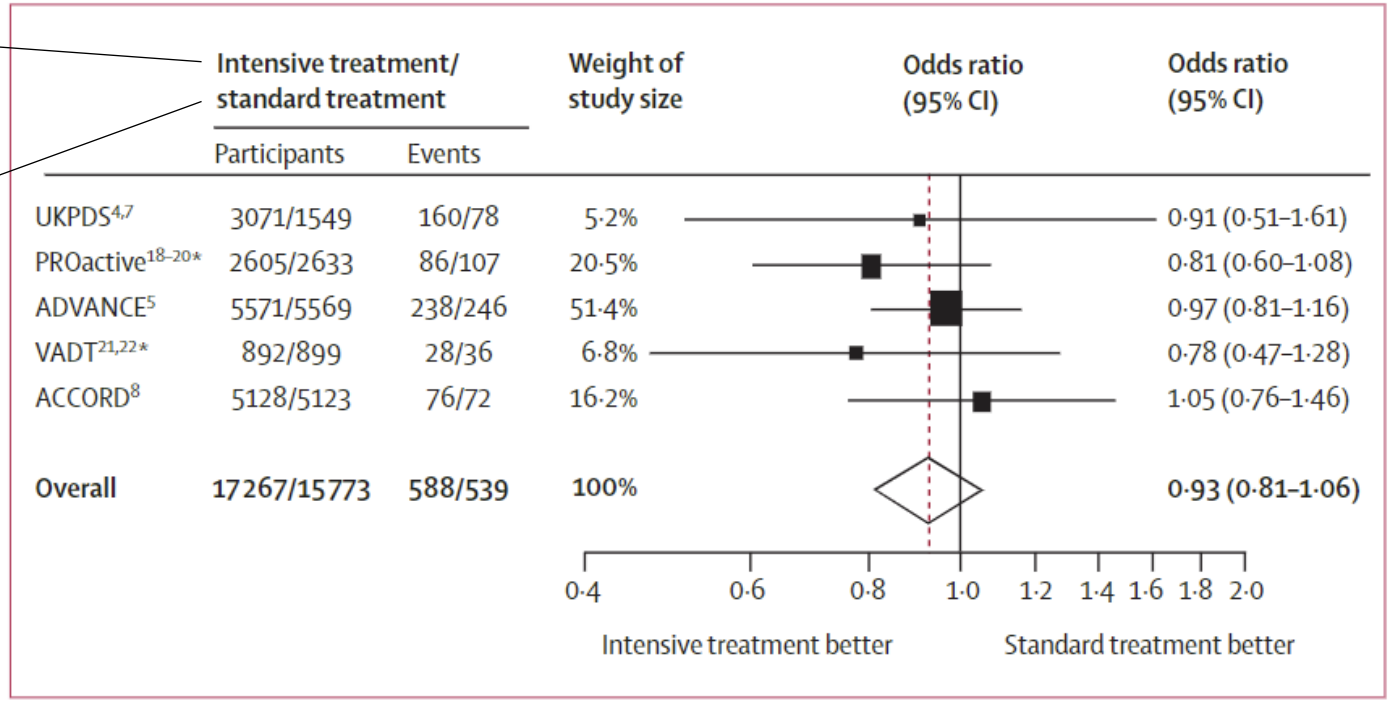


Figure 3: **Probability of events of stroke with intensive glucose-lowering versus standard treatment**
*Included only non-fatal strokes.

Lancet. 2009;373(9677):1765-1772.
BMJ. 2011;343:d4169.
Cochrane Database Syst Rev. 2013;(11):CD008143.

Table 1. (Continued.)

Characteristic	DCCT at Baseline (1983–1989)		End of DCCT (1993)		Year 11 of EDIC (2004)†	
	Intensive Treatment (N=711)	Conventional Treatment (N=730)	Intensive Treatment (N=698)	Conventional Treatment (N=723)	Intensive Treatment (N=593)	Conventional Treatment (N=589)
Glycosylated hemoglobin (%)	9.1±1.6	9.1±1.6	7.4±1.1	9.1±1.5‡	7.9±1.3	7.8±1.3

Table 2. Cardiovascular Events in Each Original Treatment Group of the DCCT.

Event	Intensive-Treatment Group			Conventional-Treatment Group		
	No. of Events	No. of Patients*	No. of Initial Events†	No. of Events	No. of Patients*	No. of Initial Events†
Death from cardiovascular disease	3	3	3	9	9	4
Nonfatal acute myocardial infarction	7	7	6	16	15	11
Silent myocardial infarction	7	7	7	21	18	13
Revascularization	17	11	4	25	20	6
Confirmed angina	11	11	10	22	18	13
Nonfatal cerebrovascular event	1	1	1	5	5	5
All cardiovascular disease events	46		31	98		52
Nonfatal myocardial infarction or stroke or death from cardiovascular disease	11		11‡	30		25‡

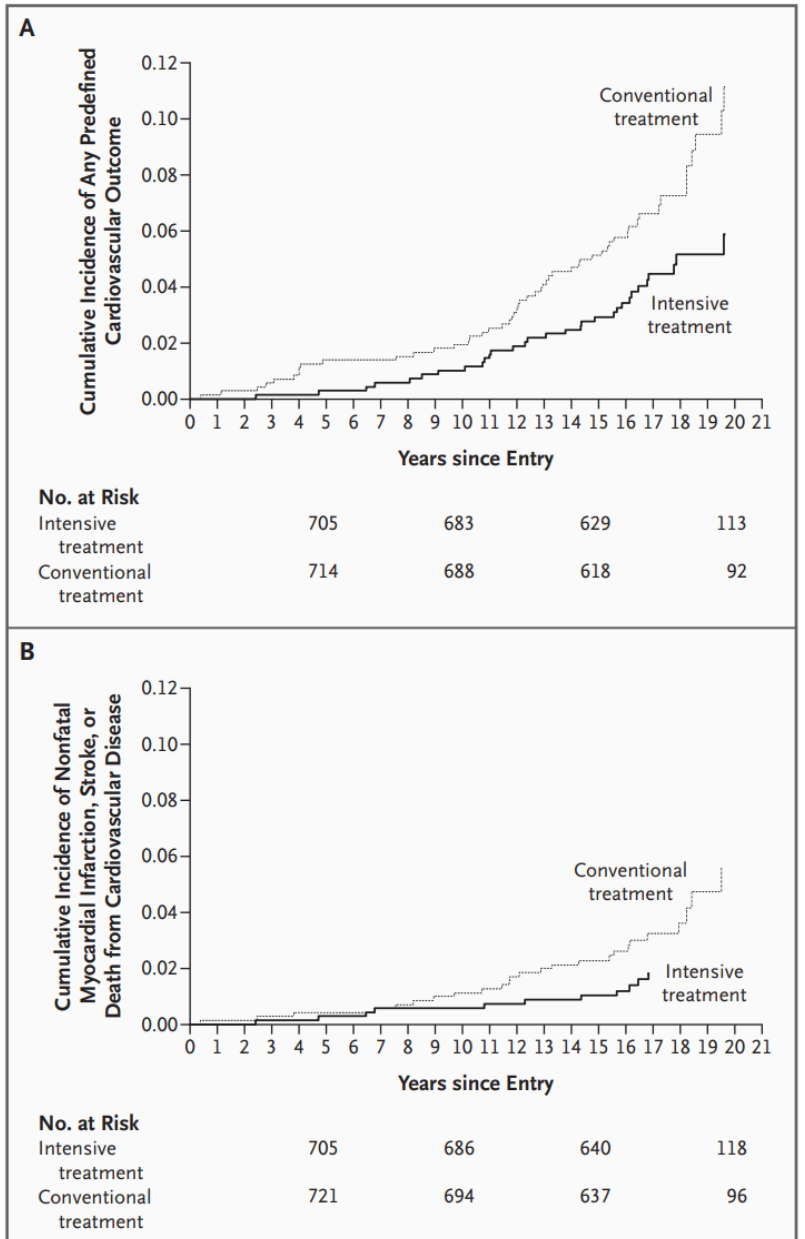


Figure 1. Cumulative Incidence of the First of Any of the Predefined Cardiovascular Disease Outcomes (Panel A) and of the First Occurrence of Nonfatal Myocardial Infarction, Stroke, or Death from Cardiovascular Disease (Panel B).

Targeting Insulin Resistance

- Nondiabetic ischemic stroke/TIA + HOMA-IR > 3
- 1:1 Pioglitazone OR Placebo
- 1° efficacy outcome: stroke/MI

N Engl J Med. 2016;374(14):1321-1331.

Table 2. Primary and Secondary Outcomes.

Outcome	Pioglitazone (N=1939)	Placebo (N=1937)	Hazard Ratio (95% CI)*	Adjusted P Value†
	no. of patients (%)			
Primary outcome				
Stroke or myocardial infarction‡	175 (9.0)	228 (11.8)	0.76 (0.62– 0.93)	0.007
Stroke	123 (6.3)	150 (7.7)		
Fatal	9 (0.5)	13 (0.7)		
Nonfatal	114 (5.9)	137 (7.1)		
Myocardial infarction	52 (2.7)	78 (4.0)		
Fatal	7 (0.4)	14 (0.7)		
Nonfatal	45 (2.3)	64 (3.3)		
Secondary outcome§				
Diabetes mellitus	73 (3.8)	149 (7.7)	0.48 (0.33–0.69)	<0.001
Death from any cause	136 (7.0)	146 (7.5)	0.93 (0.73–1.17)	0.52

Table 3. Adverse Events, According to Severity.*

Event	Pioglitazone (N=1939)	Placebo (N=1937)	P Value
	no. of patients (%)		
Other adverse event			
Bone fracture¶	133 (6.9)	94 (4.9)	0.008
Heart failure¶	29 (1.5)	32 (1.7)	0.70
Weight gain			
>4.5 kg	1013 (52.2)	653 (33.7)	<0.001
>13.6 kg	221 (11.4)	88 (4.5)	<0.001
Edema‖	691 (35.6)	483 (24.9)	<0.001
Shortness of breath	342 (17.6)	292 (15.1)	0.03
Alanine aminotransferase >ULN	26 (1.3)	59 (3.0)	<0.001
Macular edema	3 (0.2)	2 (0.1)	0.66

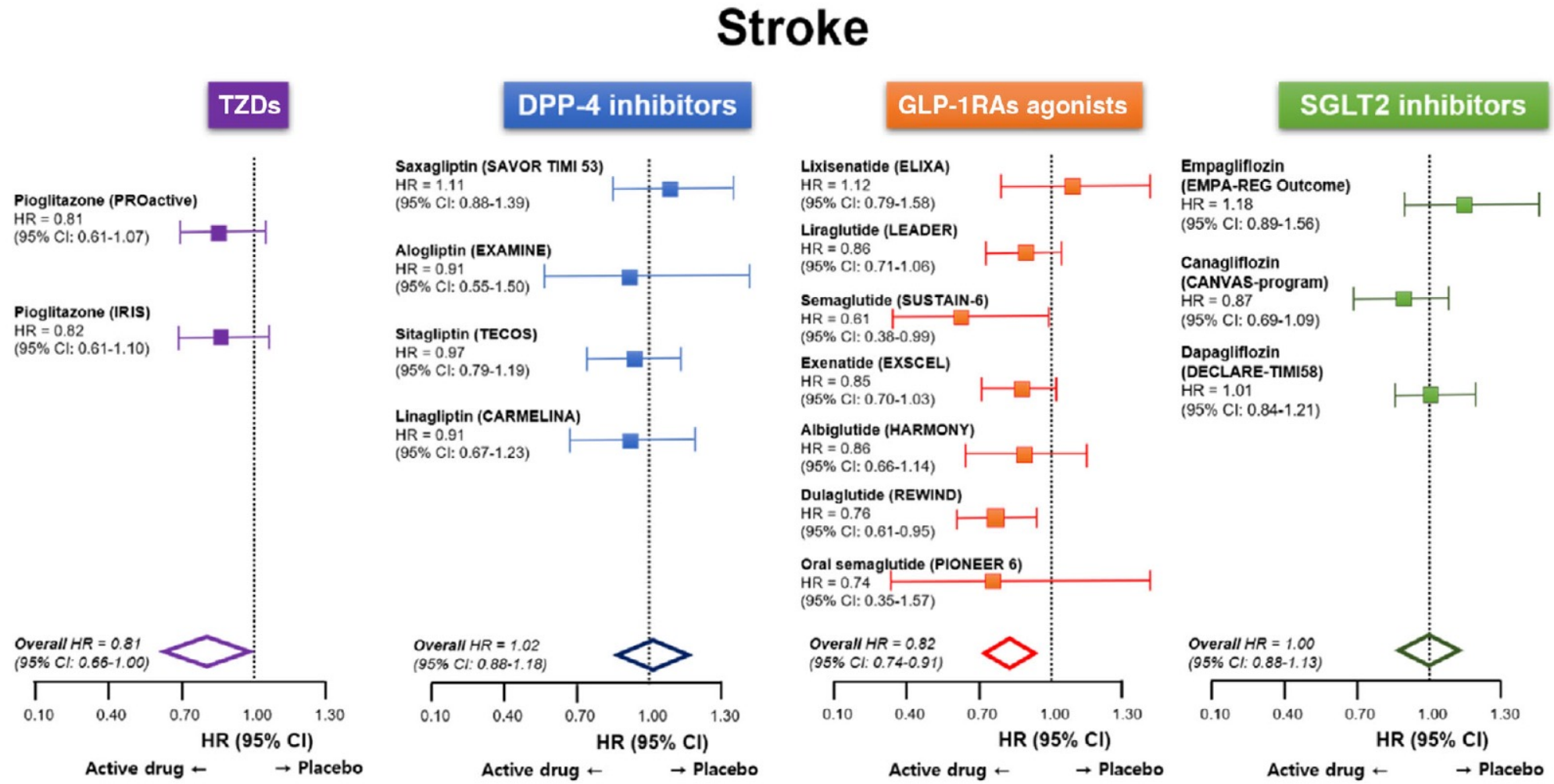


FIGURE 2 Individual and overall effects of thiazolidinediones (TZDs) and new antidiabetic agents on primary cardiovascular (CV) outcome and stroke. The hazard ratios (HRs) with 95% confidence intervals (CIs) are given for active drug compared with placebo. Primary CV outcomes are slightly different in each study

Diabetes Obes Metab. 2020;22(1):6-15.

Hypertension

- Observational studies, RCTs, meta-analyses → <130/80
- CCB, ARB/ACEi

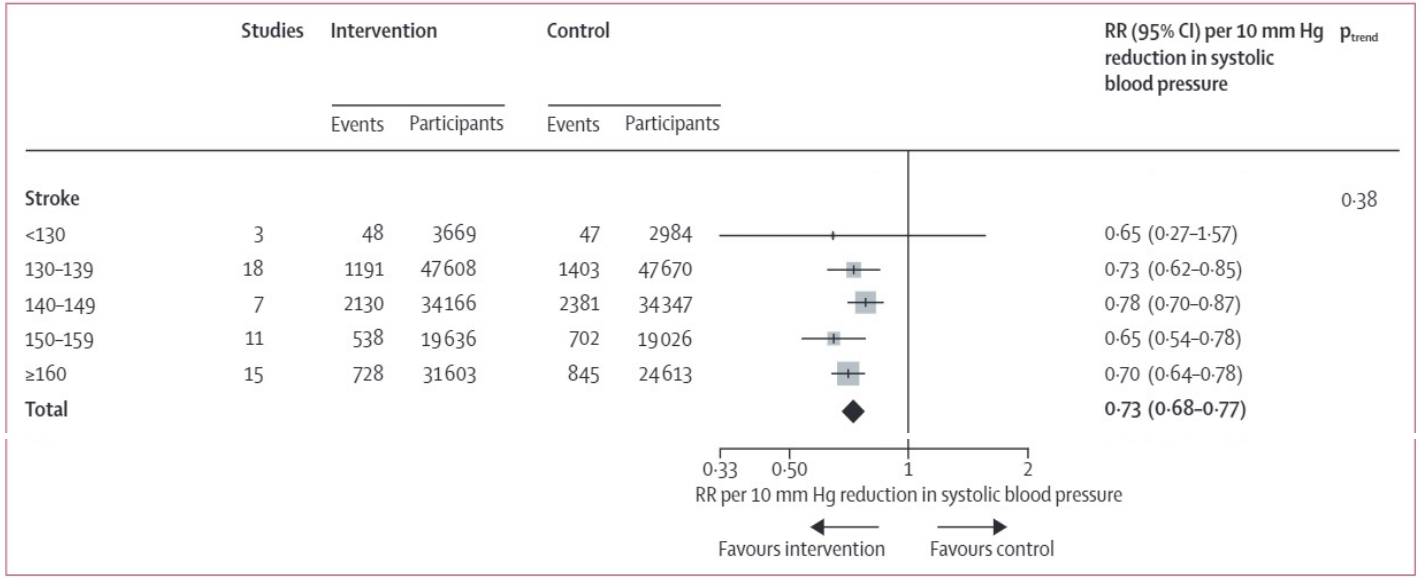


Figure 4: Standardised effects of a 10 mm Hg reduction in systolic blood pressure stratified by blood pressure
Blood pressure strata are baseline blood pressure values, not achieved blood pressure after treatment. RR=relative risk.

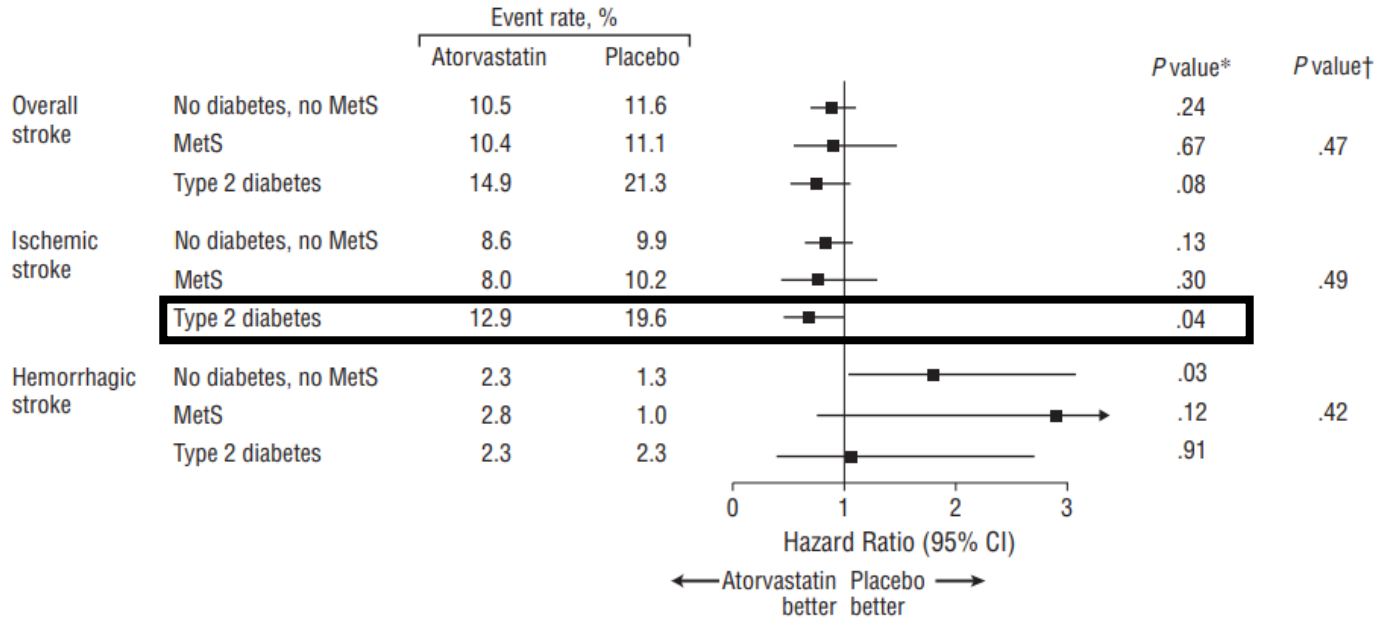
Table 3. Primary and Secondary Outcomes.

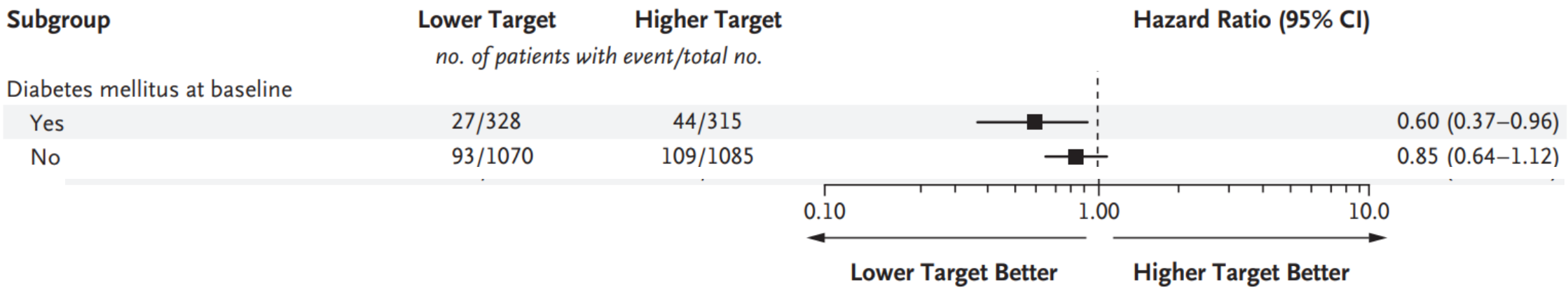
Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03

N Engl J Med. 2010 Apr 29;362(17):1575-85.
JAMA. 2015;313(6):603-615.
Lancet. 2016;387(10022):957-967.

Lipids

- Target LDL<70 mg/dL
  - high-intensity statin therapy
    - +/- Ezetimibe
    - PCSK9 inhibitor therapy





Arch Neurol. 2011 Oct;68(10):1245-51.
N Engl J Med. 2020;382(1):9.

Antithrombotic Therapy

TABLE 3 Multivariate Model Showing the Benefit of Clopidogrel Over Aspirin in Reducing Death, Myocardial Infarction (MI), Stroke, or Rehospitalization for Ischemia or Bleeding After Adjustment for Baseline Characteristics

Variable	Risk Ratio	p Value
Clopidogrel	0.869	0.032
Age	1.103/10 yrs	0.012
Angina	1.559	0.001
Prior stroke	1.246	0.072
Prior MI	1.236	0.020
Claudication	1.732	0.001

Atrial Fibrillation → Apixaban, Rivaroxaban, Dabigatran efficacy/risks similar in diabetics and non-diabetics

Am J Cardiol. 2002;90(6):625-628.
BMJ. 2002;324(7329):71-86.
N Engl J Med. 2009;361(12):1139-1151.
N Engl J Med. 2011;365(10):883-891.
N Engl J Med. 2011;365(11):981-992.

Symptomatic Carotid Stenosis

- Endarterectomy → benefits and risks may be higher in diabetics
- Restenosis risk higher (after CEA or CAS)

	No restenosis (n=2071)	Restenosis (n=120)	p value for group differences in composite endpoint	Univariate HR (95% CI)	Multivariable HR (95% CI)*	Most parsimonious model HR (95% CI)
Carotid artery stenting	1028/2071 (50%)	58/120 (48%)	0·781	0·94 (0·65–1·34)	0·94 (0·65–1·37)	..
Age (years)	69·0 (8·8)	67·1 (9·6)	0·025	0·80 (0·66–0·98)	0·92 (0·73–1·17)	..
Women	686/2071 (33%)	56/120 (47%)	0·0023	1·75 (1·23–2·51)	1·83 (1·26–2·67)	1·79 (1·25–2·56)
White	1945/2071 (94%)	112/120 (93%)	0·7957	0·82 (0·40–1·68)	0·89 (0·43–1·86)	..
Symptomatic	1105/2071 (53%)	54/120 (45%)	0·0746	0·74 (0·51–1·05)	0·86 (0·58–1·28)	..
Hypertension†	1757/2069 (85%)	111/120 (93%)	0·0225	2·16 (1·09–4·25)	1·57 (0·78–3·14)	..
Diabetes‡	607/2066 (29%)	60/120 (50%)	<0·0001	2·39 (1·67–3·42)	2·22 (1·52–3·26)	2·31 (1·61–3·31)
Dyslipidaemia§	1751/2062 (85%)	111/119 (93%)	0·0121	2·34 (1·14–4·80)	1·97 (0·90–4·31)	2·07 (1·01–4·26)
Present smoker	534/2041 (26%)	39/118 (33%)	0·0995	1·38 (0·94–2·03)	1·47 (0·95–2·27)	..
Previous cardiovascular disease or coronary artery bypass graft	909/2007 (45%)	56/114 (49%)	0·4242	1·18 (0·82–1·71)	1·07 (0·73–1·57)	..
Pretreatment stenosis of at least 70%	1779/2071 (86%)	105/120 (88%)	0·624	1·15 (0·67–1·97)	1·07 (0·6–1·93)	..
Treatment within 7 days of randomisation	1190/2071 (58%)	59/120 (49%)	0·0744	0·73 (0·51–1·04)	0·78 (0·53–1·15)	..
Antiplatelet treatment	1928/2046 (94%)	110/117 (94%)	0·9226	0·94 (0·44–2·01)	0·93 (0·43–2·01)	..

Lancet. 2004;363(9413):915-924.
Lancet Neurol. 2012;11(9):755-763.
Cochrane Database Syst Rev. 2017;6(6):CD001081.

Diabetes and Cognitive Impairment

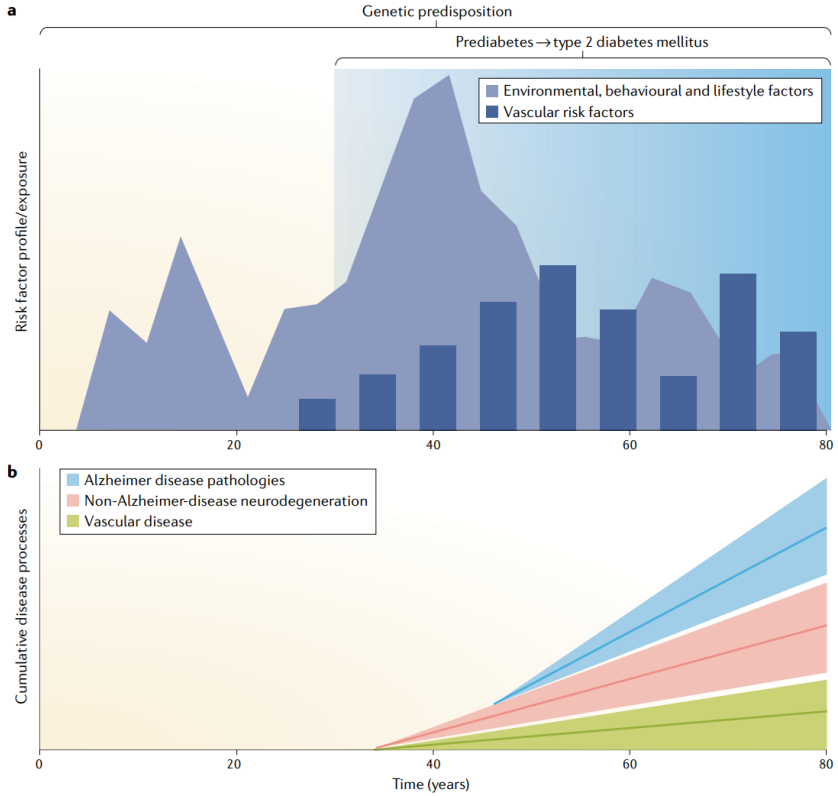


Fig. 2 | **Risk factors and underlying pathologies for dementia in type 2 diabetes mellitus.** The figure provides a life

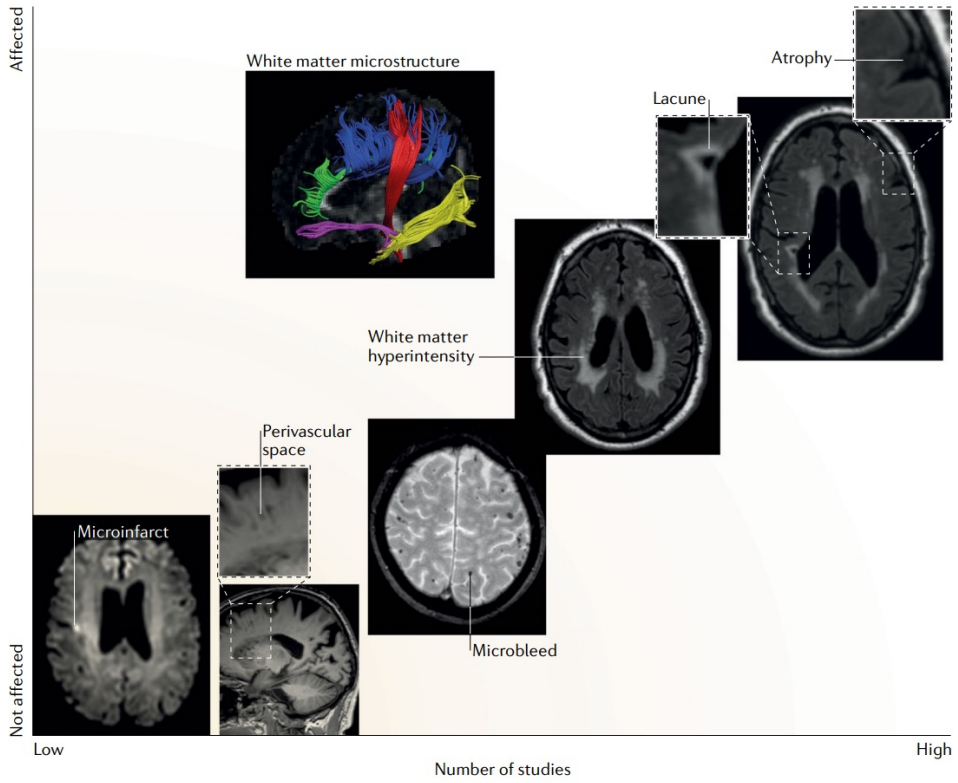


Fig. 1 | **Brain imaging findings in patients with type 2 diabetes mellitus.** The figure summarizes findings on structural

Nat Rev Endocrinol. 2018;14(10):591-604.

Future Directions

- Interaction of DM with (established and emerging) stroke risk factors, mediators of atherosclerotic stroke and lacunar infarction
  - lipidome
  - inflammatory mediators
- Mechanisms of cerebral microvascular dysfunction → predictive & therapeutic biomarkers, novel therapeutics
- Glucagon-like peptide 1 receptor agonists

Key Points

- Diabetes increases ischemic stroke risk 2-fold
  - Insulin resistance (nondiabetics) & prediabetes
  - All subtypes – especially lacunar infarction
- Less robust & inconsistent evidence linking diabetes and ICH
- Diabetes & poststroke hyperglycemia are associated with worse outcomes
- Intensive blood glucose control does not improve functional outcomes (acute stroke) or reduce stroke risk → other processes impact stroke risk
- A multifactorial risk factor management strategy is important for stroke prevention

Questions?