The Leeds Teaching Hospitals NHS
NHS Trust

The Influence of Diabetes on the Efficacy of Aspirin Therapy

Glucose Control and Acetyl Salicylic Acid

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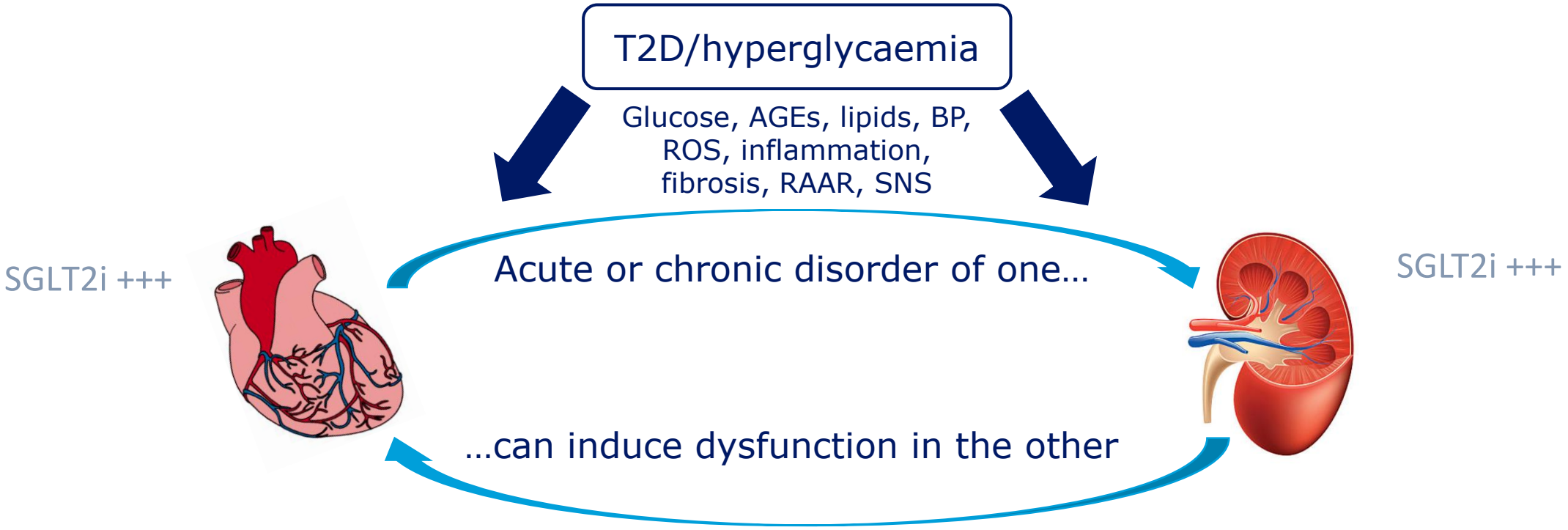
Disclosures

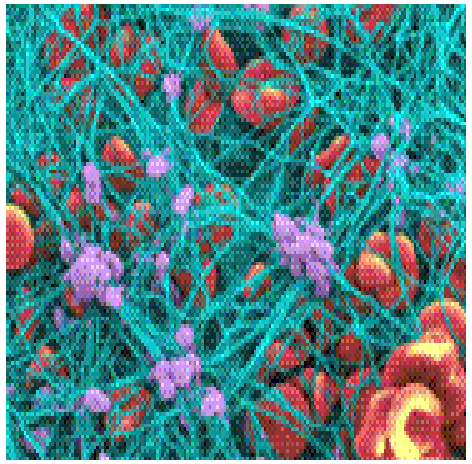
- Speaker for GSK, Astra Zeneca, Takeda, Medicines Company, Merck, Novo Nordisk
- Advisory boards for Amgen, Novartis, Novo Nordisk, Astra Zeneca
- Diabetes adviser, Synexus
- Editor in Chief, Diabetes and Vascular Disease Research
- Co-chair ESC/EASD guidelines on CVD in Diabetes 2007-20

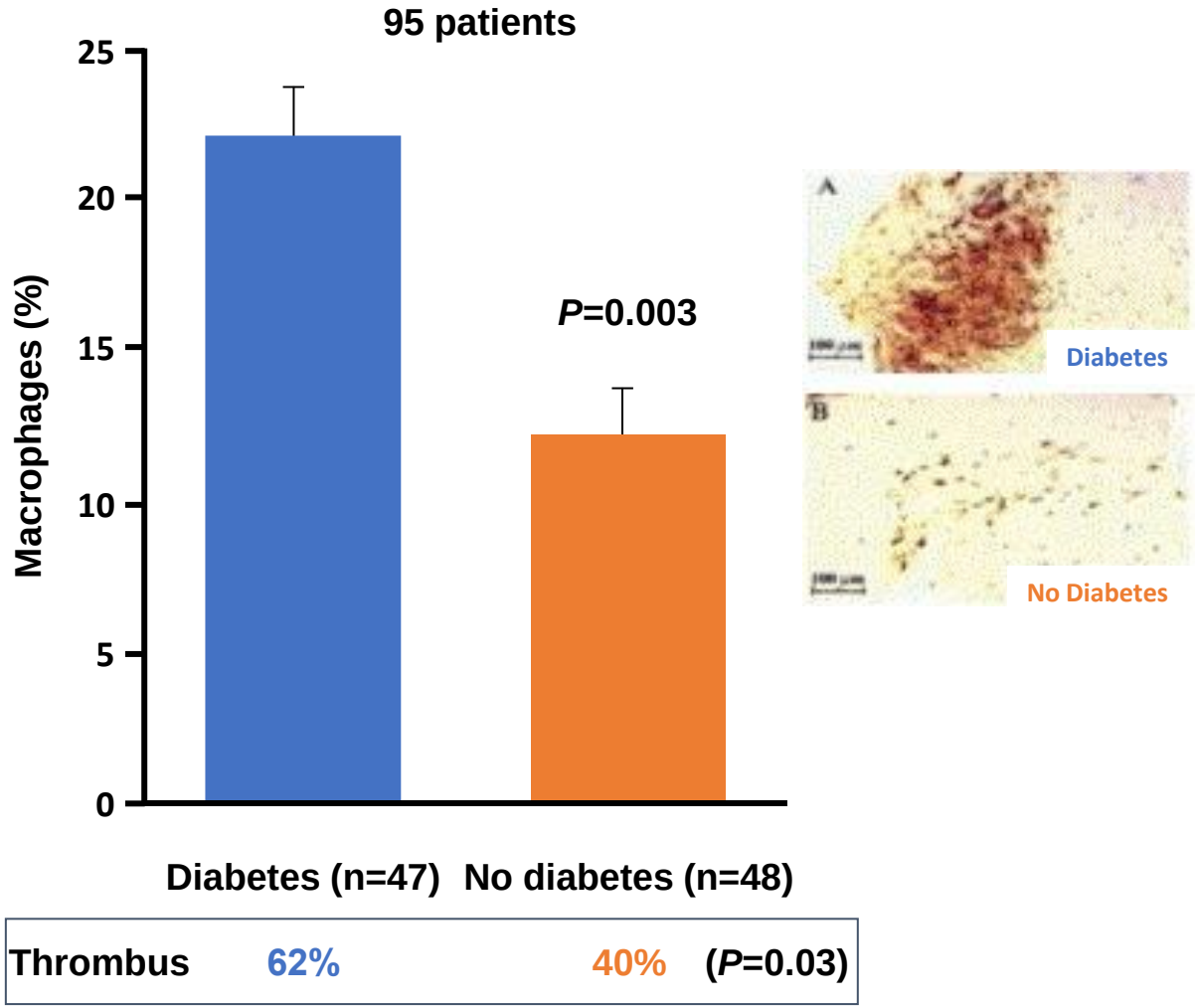
Diabetes, CVD and Renal Disease: The Deadly Triad



Coronary Composition in Atherectomy Specimens from Patients with Diabetes Mellitus

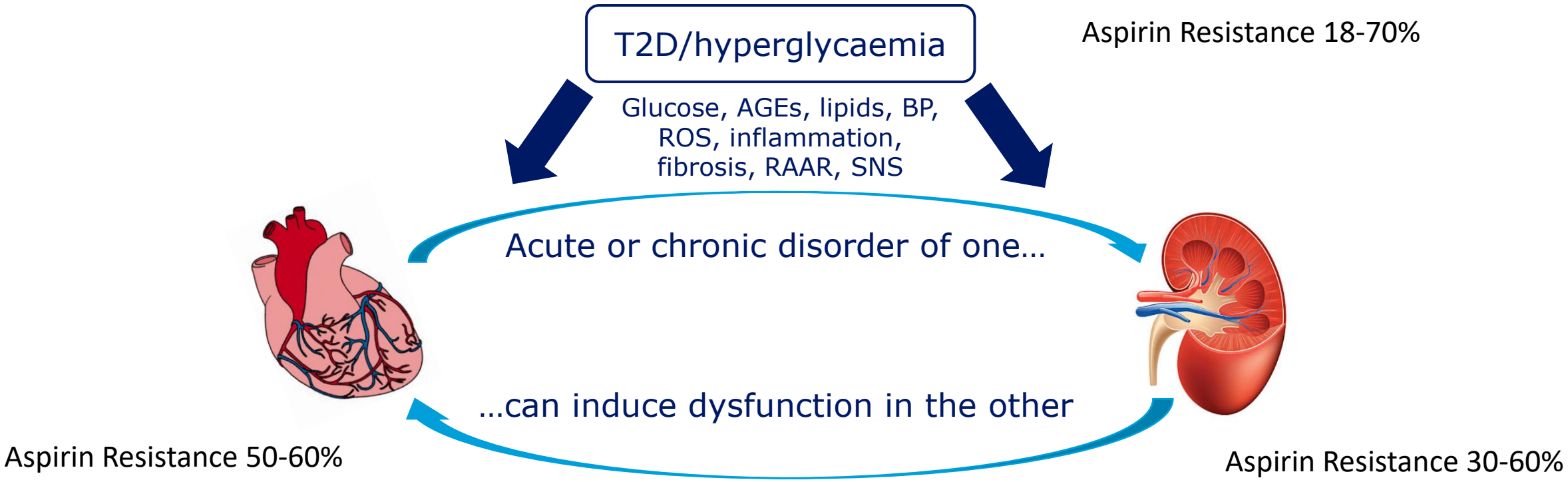
- Greater area of lipid-rich atheroma
- Macrophage infiltration
- More thrombus





Moreno, et al. *Circulation* 2000

Aspirin Resistance in The Deadly Triad



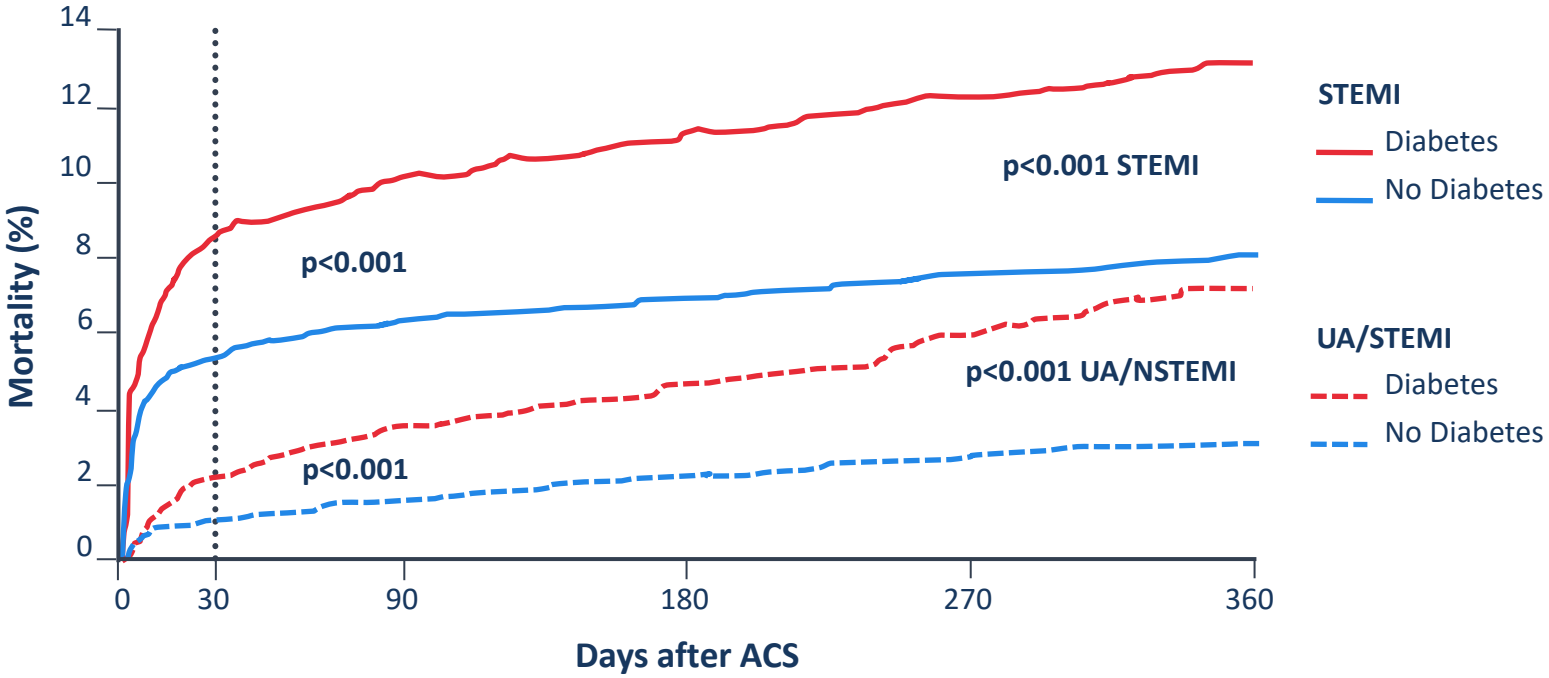
Ebrahimi P, et al Caspian J Intern Med. 2020;11(2):124-134
Guirgis M et al J Vasc Surg 2017 Nov;66(5):1576-1586.

A Randomised Trial of Aspirin versus Placebo for Primary Cardiovascular Prevention in 15,480 people with Diabetes (ASCEND)

- Aspirin 100 mg/day vs placebo
- Serious vascular events (SVE) followed for 7.4 years
- Safety assessed by bleeding
- Small reduction in SVE
- Hazard ratio 1.3 for major bleeding
- Aspirin not warranted in primary prevention in diabetes

Armitage J et al ESC Munich Sept 2018

Diabetes and Mortality Through 1 Year After ACS: Residual Risk



11 TIMI trials with >62,000 patients (10,613 diabetics; 17.1%)

Donahoe et al. JAMA 2007;298:765–75

Fluid and Cellular Components of Thrombosis

Fluid

Coagulation proteins
- Thrombin
- Fibrinogen
- Factor XIII

Fibrinolysis
- Plasmin
- PAI-1
- tPA

Cellular

Platelets
- Endothelium
- Macrophages

Fibrin Formation

Fibrin breakdown

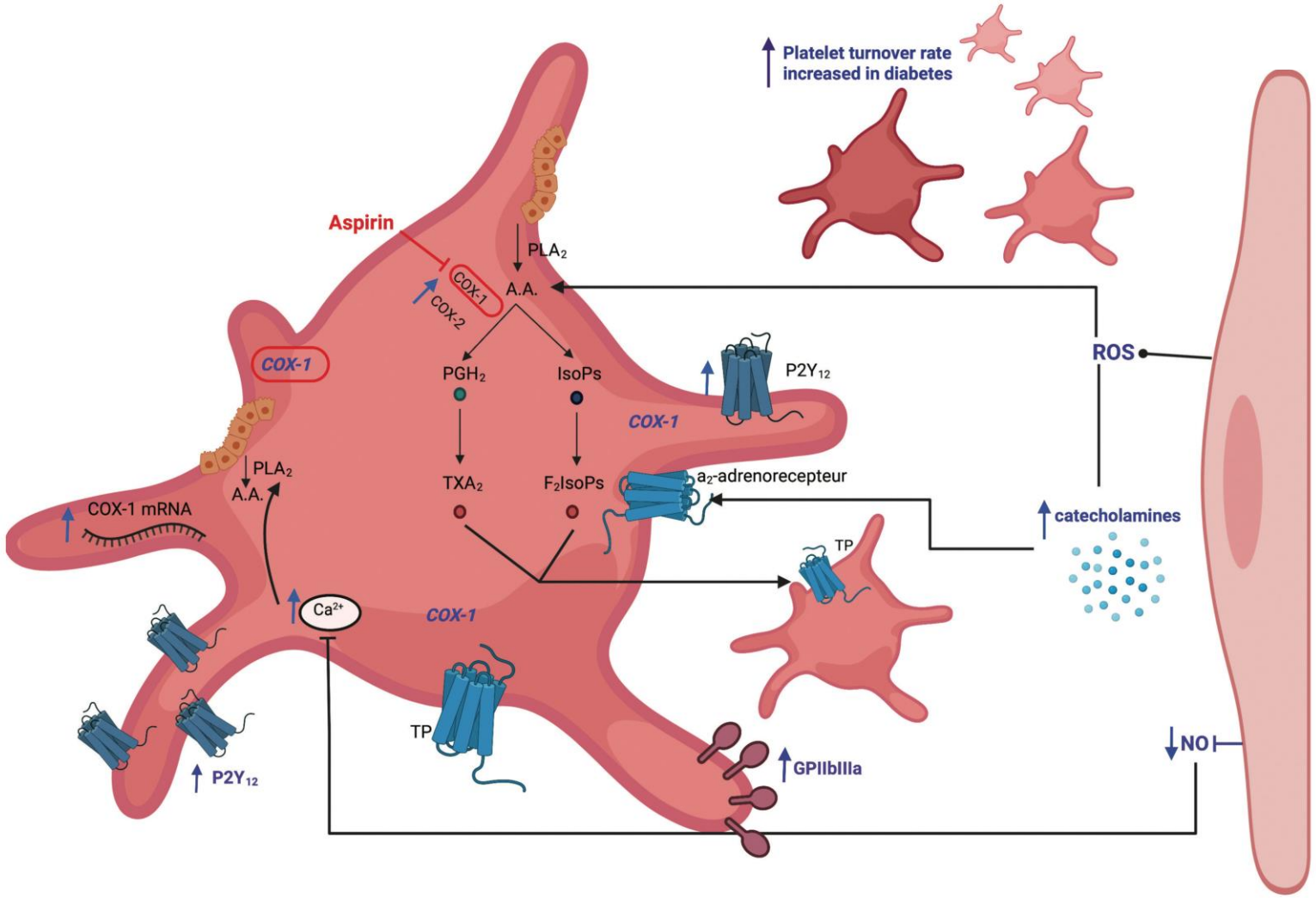
Platelet adhesion/aggregation

Therapeutic Effects of Aspirin on Thrombosis

- Irreversible inhibitor of COX enzymes in the platelet
- Blocks thromboxane A2 production to inhibit platelet aggregation and vasoconstriction.
- Acetylates fibrinogen to produce a fibrin network that is easier to lyse.
- Aspirin acts clinically to reduce secondary acute coronary syndromes
- Efficacy in primary prevention is questionable
- Generally less effective in diabetes than non- diabetes subjects

The Hyperactive Platelet in Diabetes

- Systemic inflammation
- COX2 activation
- COX1/albumin glycation
- Endothelial dysfunction
- Oxidative stress
- Insulin resistance
- Dyslipidaemia
- Hyperglycaemia



Mélina Del Bianco-Rondeau et al Thromb Haemostas 2022

Platelet and Myeloid Precursors in Diabetes

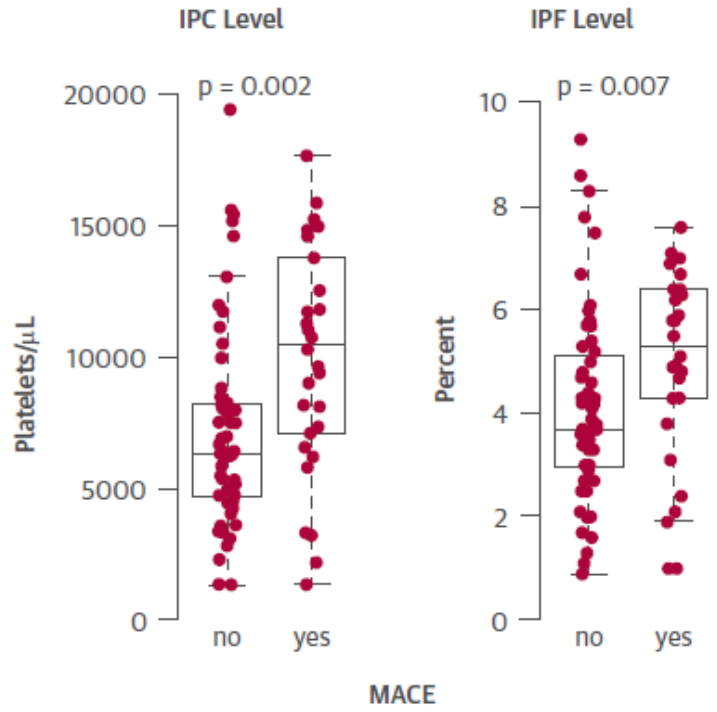
- Abnormal myelopoiesis related to poor glycaemic control
- More rapid turnover of platelets
- Raised platelet count
- Increased mean platelet volume
- Increased immature reticulated thrombocytes which circulate in a activated state

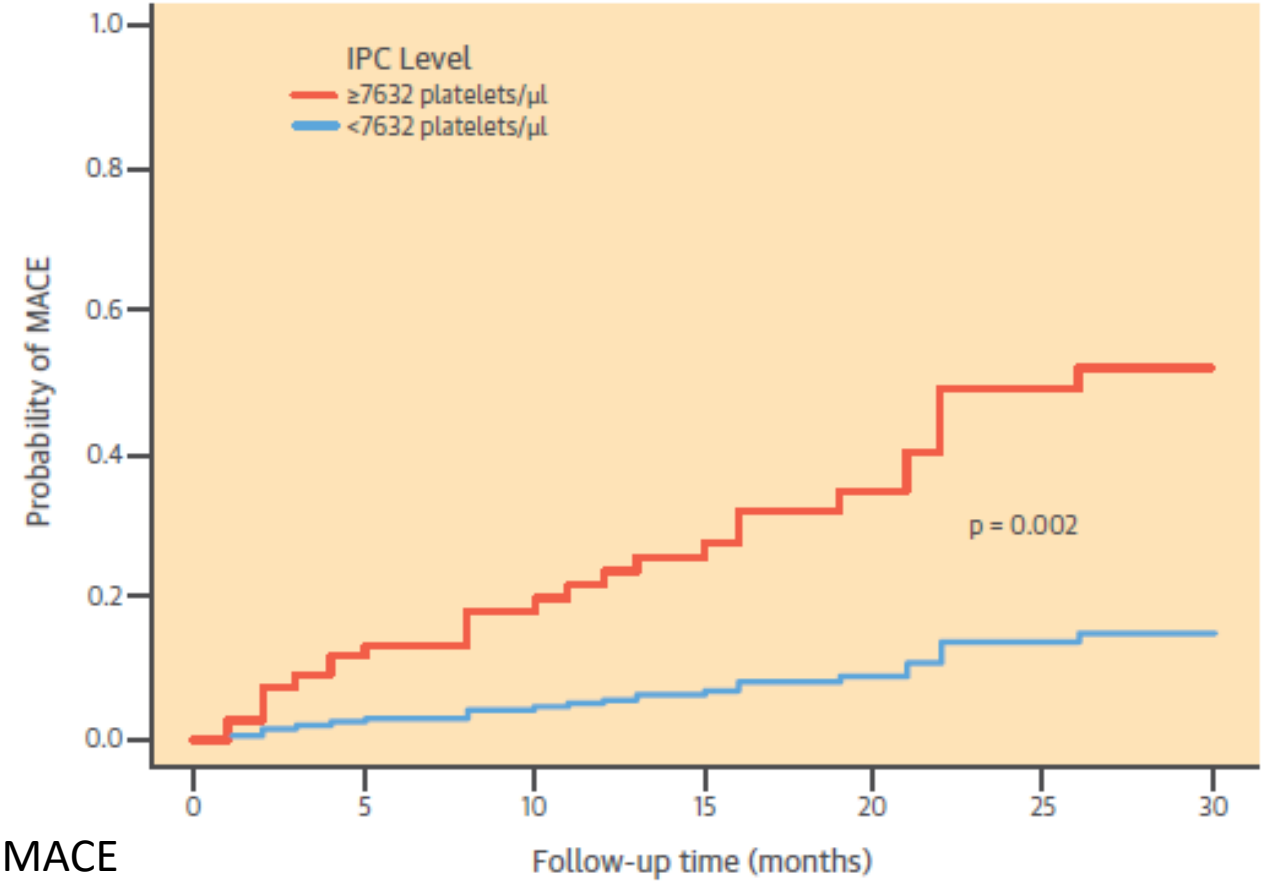
Nagareddy PR et al Cell Metab 2013, 695-708
Kraakman MJ et al J Clin Invest 2017, 2133-47

Reticulated Platelets

- An incompletely developed platelet in the circulation that contains strands of mRNA or rRNA.
- Small numbers of reticulated platelets, typically less than 5%, are found in blood as a result of normal maturation from bone marrow megakaryocytes.
- High levels of reticulated platelets appear in disorders in which platelets are rapidly destroyed, such as idiopathic thrombocytopenic purpura or disseminated intravascular coagulation.
- Increased numbers in diabetes regulated by glycation

Association of Immature Platelets with Adverse Cardiovascular Outcomes





- IPC >7632/uL was 70% sensitive and 82% specific for MACE
- Hazard ratio 4.65 (1.8-12.2)

Ibrahim H et al JACC 2016, 219-27

Increased Reticulated Platelets Associate with Resistance to Aspirin and Clopidogrel

- Newly released platelets more likely to participate in thrombosis
- Reticulated platelet count provides an indicator of platelet maturity
- Reticulated platelet counts predict resistance to aspirin and clopidogrel in volunteers and CAD patients
- Up to 50% of those in the upper tertile of reticulated platelet counts were resistant to antiplatelet therapy
- In ExcelsiorLOAD, reticulated platelet count was the strongest predictor of resistance to loading clopidogrel or prasugrel doses in PCI

Kleiman NS JACC, 2016, 294-6
Karpatkin S, J Clin Invest, 1969, 1083-7
Guthikonda S et al, JACC, 2008, 743-9
HochholzerW et al, JACCIntv 2016,219-27

The Role of Albumin in the Regulation of Platelet Aggregation

- Albumin is an acute phase reactive protein with antioxidant and antiplatelet activity *in vitro*.
- Albumin dose-dependently inhibits platelet aggregation with a Nox2-related oxidative stress mechanism *in vitro*
- Albumin supplementation in humans impairs platelet aggregation.
- Albumin <3.5 g/dL is associated with an increased risk of arterial and venous thrombosis
- In diabetes, albumin glycation, results in a 50% higher fraction of unbound aspirin

Belinskaia D. A., et al Antioxidants. 2020 9 (10), 966–994
Chi G., et al(2019). Am. J. Hematol. 2019; 94 (1), 21–28.
Basili S. et al, Hepatol. Commun. 2019; 3 (4), 504–512.

Impaired Clinical Efficacy of Aspirin in Hypoalbuminemic Patients with Diabetes Mellitus

	Number of patients (number of events per 100 patient-year)			
	All (*n*= 612)	Albumin <3.5 g/dL (*n* = 250)	Albumin ≥3.5 g/dL (*n* = 362)	*p*value
Total mortality, *n (%)*	10 (0.36)	6 (0.54)	4 (0.24)	0.214
CVEs, *n (%)*	86 (3.10)	49 (4.39)	37 (2.24)	0.001
Cardiovascular mortality, *n (%)*	7 (0.25)	4 (0.36)	3 (0.18)	0.377
Nonfatal cardiovascular events, *n (%)*	79 (2.85)	45 (4.02)	34 (2.05)	0.001
Coronary, *n (%)*	65 (2.34)	37 (3.31)	28 (1.69)	0.005
Cerebrovascular, *n (%)*	14 (0.50)	8 (0.72)	6 (0.36)	0.209
Follow-up, *months*	54.4 ± 7.3	53.7 ± 7.2	54.8 ± 7.4	0.067

Sciacqua A, Andreozzi F, Violi F, Frontiers in Pharmacology 2021

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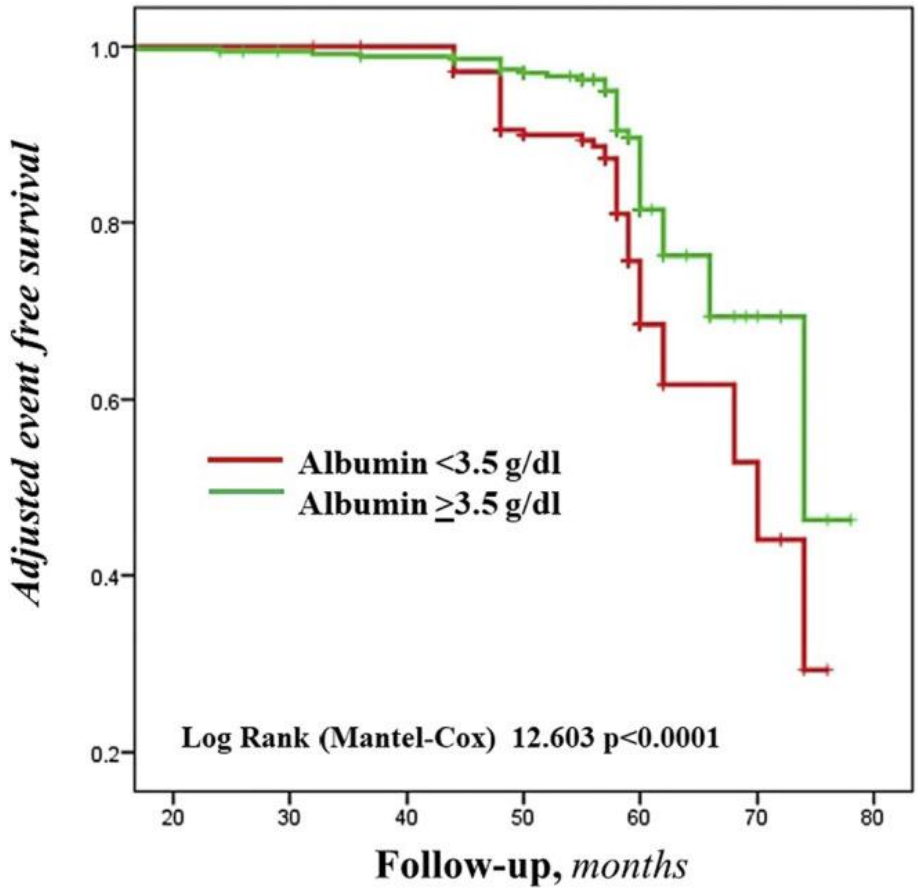
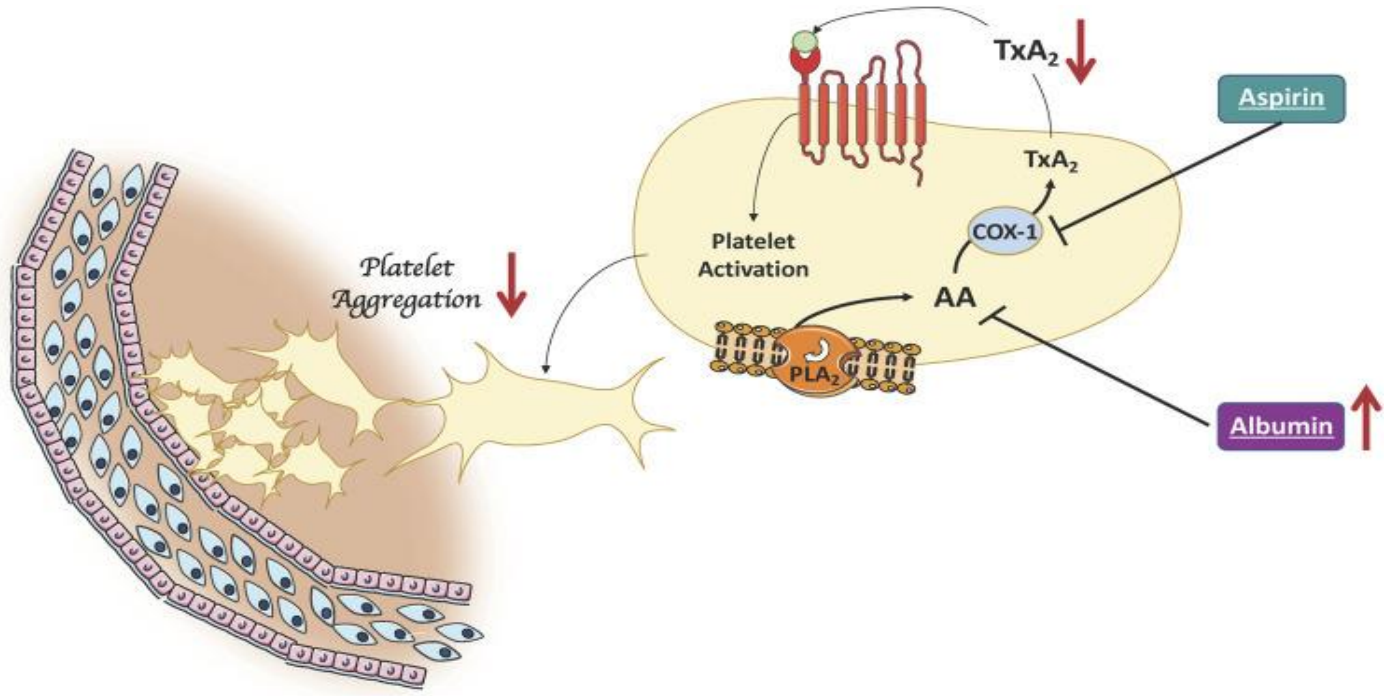


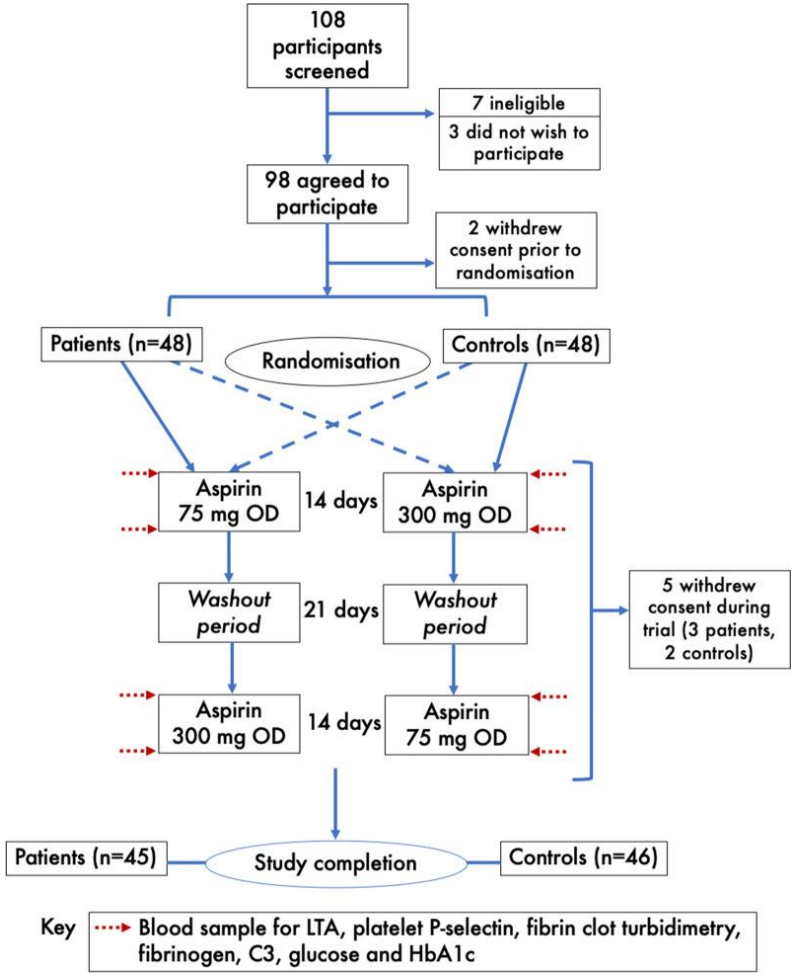


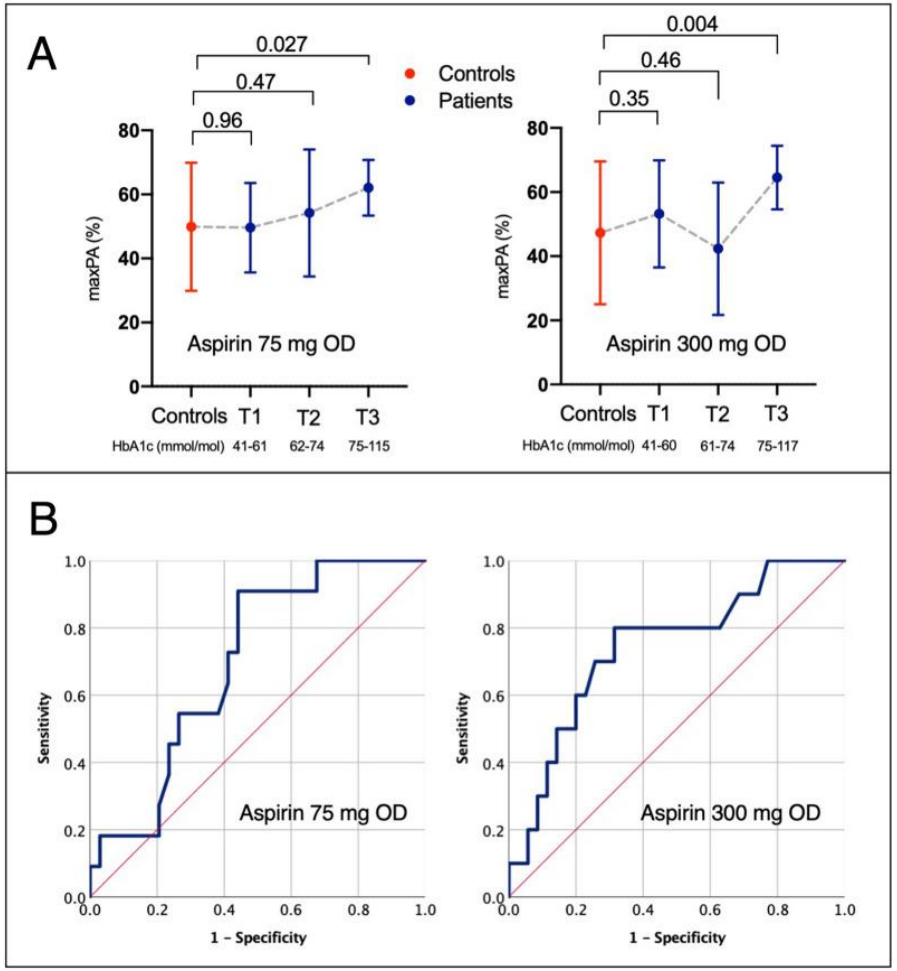
Sciacqua A, Andreozzi F, Violi F, Frontiers in Pharmacology 2021

The Role of Glucose/Glycation in Thrombosis

- Fibrinogen glycation creates a rigid fibrin structure
- Plasminogen glycation inhibits plasmin generation and clot lysis
- Albumin glycation alters aspirin bioavailability
- COX-1 glycation impairs aspirin inhibition
- Glycation increases production of reticulated platelets
- All effects compounded by risk factor cluster, end organ damage

The antithrombotic effects of aspirin in type 1 diabetes: role of dosing and glycaemic control





Parker WAE et al Cardiovascular Diabetology (2021) 20:238

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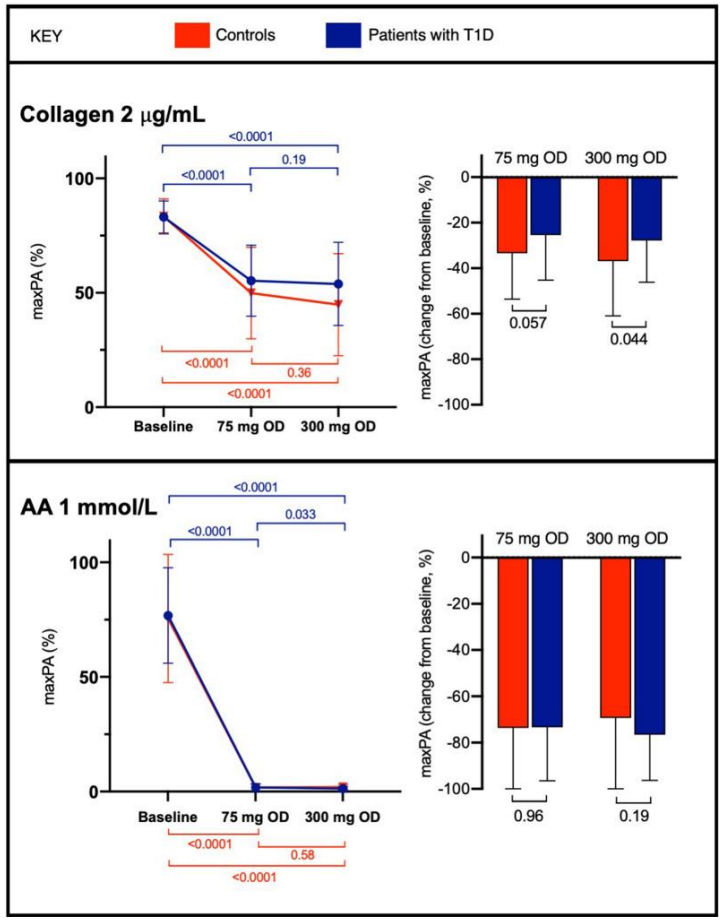

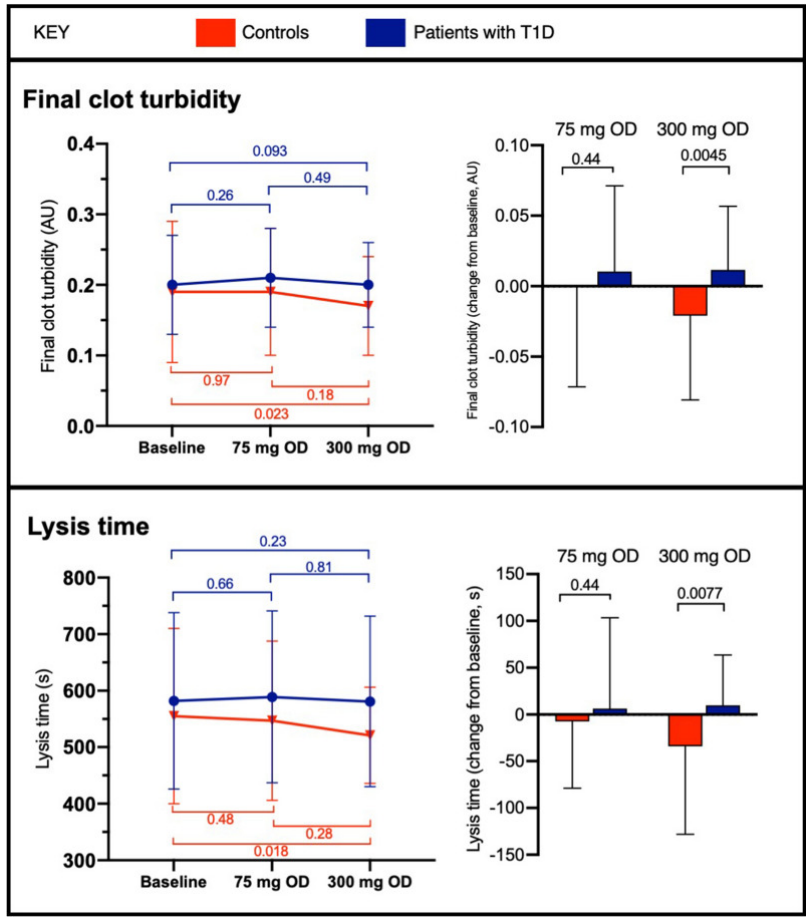

Parker WAE et al Cardiovascular Diabetology (2021) 20:238

Managing Aspirin Resistance in Diabetes

- Improve glycaemic control on an individualized basis
- Intensive management of cardiovascular risk factors
- Management of obesity
- Twice daily aspirin regimens
- Potential role for non enteric coated formulations
- Use aspirin according to risk
- Addition of a second agent

Twice daily dosing of aspirin improves platelet inhibition in whole blood in patients with type 2 diabetes mellitus and micro- or macrovascular complications

- A randomised cross-over study compared 75 mg aspirin OD, 75 mg BID and 320 mg OD in 25 patients with T2DM and micro- or macrovascular complications.
- Aspirin 75 mg BID decreased arachidonic acid (AA)-induced impedance aggregometry compared to 75 mg OD (9.7 ± 4.5 vs. 12.6 ± 3.5 ohm; p = 0.003) or to 320 mg OD (11.5 ± 4.2 p = 0.049).
- WBA responses to collagen were similarly attenuated by BID or high dosing (by 12-14%; p = 0.02 for both).
- The IMPACT-R in whole blood showed a better response to 75 mg BID compared to 75 mg OD (p = 0.049), but not to 320 mg OD.
- Twice daily dosing improved laboratory responses to aspirin in high risk T2DM patients.

SpectreG, et al Thromb Haemost. 2011; 106(3):491–499.

Enteric Coated Aspirin Formulations

- In ASCEND, all patients received an EC aspirin formulation
- EC absorption is erratic, particularly with gastroparesis
- In a randomized crossover study in 71 healthy volunteers, incomplete platelet inhibition, was significantly higher in the EC group (54.3%) than in the dispersible aspirin group (8.0%).
- Diabetes patients (n=30) expressing an aspirin resistance phenotype with EC aspirin 100 mg daily , were switched to an infusion of lysine acetylsalicylate. Only three patients (10%) demonstrated ASA resistance
- Emerging evidence that obesity may limit the efficacy of EC aspirin

Grimaldi R, et al. Cardiovasc Drugs Ther 2014;28 (04):323–329
Rocca B, Fox KAA, Ajjan RA, et al. Eur Heart J 2018;39(19):1672–1686f

Cardiovascular risk categories in patients with DM

Very high-risk	Patients with DM **and** established CVD **or** other target organ damage[a] **or** three or more major risk factors[b] **or** early onset T1DM of long duration (>20 years)
High-risk	Patients with DM duration ≥10 years without target organ damage[a] plus any other additional risk factor[b]
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors

[a] proteinuria, renal impairment defined as eGFR≥30mL/min/1.73m^2.
[b] age, hypertension, dyslipidemia, smoking, obesity.

Cosentino F, Grant PJ, et al, Eur Heart J. 2020;41(2):255-323.

Recommendations for antiplatelet therapy in primary prevention in DM

Recommendations	Class	Level
In patients with DM at high/very high risk, aspirin (75–100 mg/day) may be considered in primary prevention in the absence of clear contraindications.	IIb	A
In patients with DM at moderate CV risk, aspirin for primary prevention is not recommended.	III	B
Gastric protection		
When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding.	IIa	A

Cosentino F, Grant PJ, et al, Eur Heart J. 2020;41(2):255-323.