Overcoming the Barriers of Atherothrombotic Risk: The Challenge on the Management of Diabetic Patients

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Disclosures for Freek W. A. Verheugt

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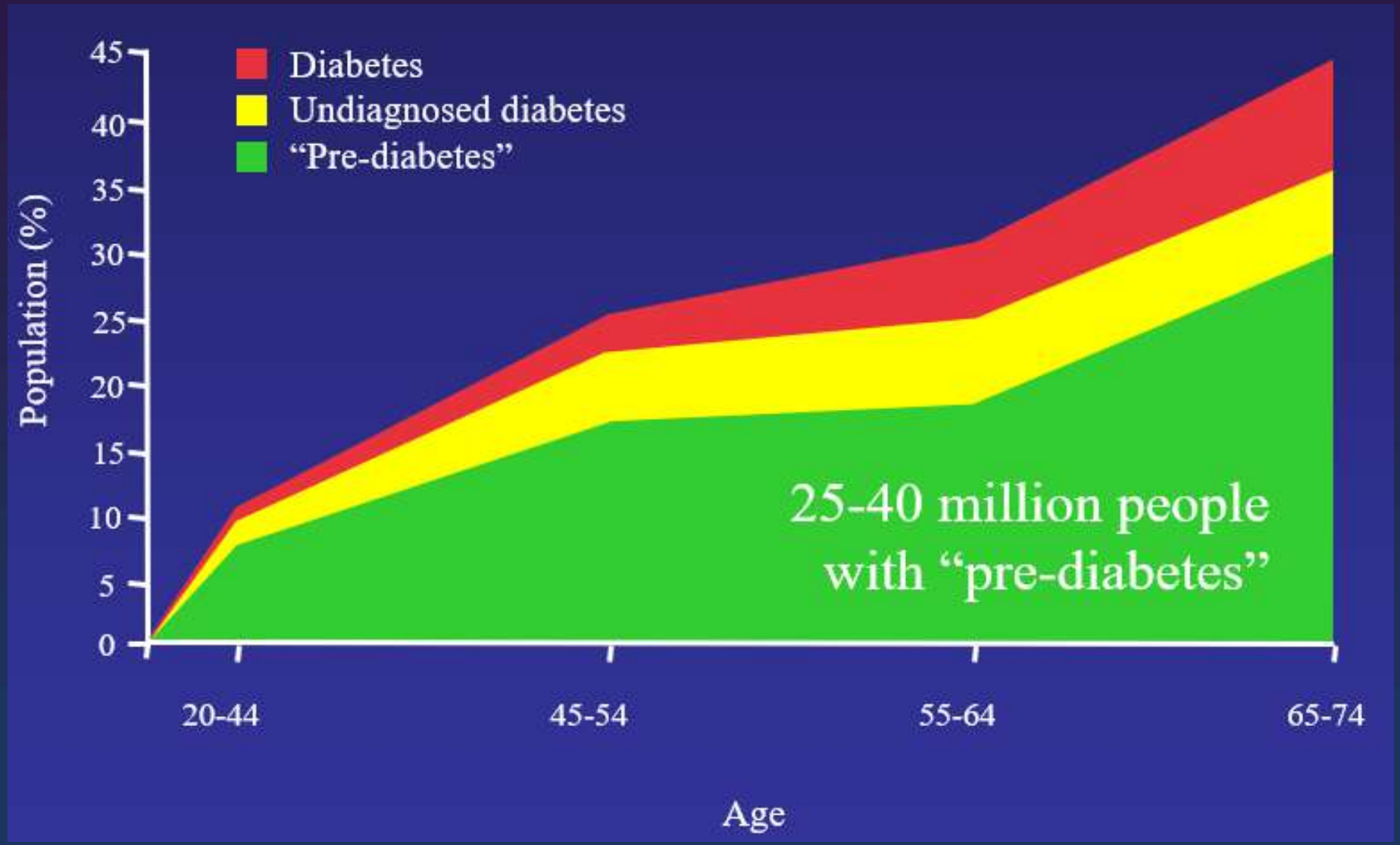
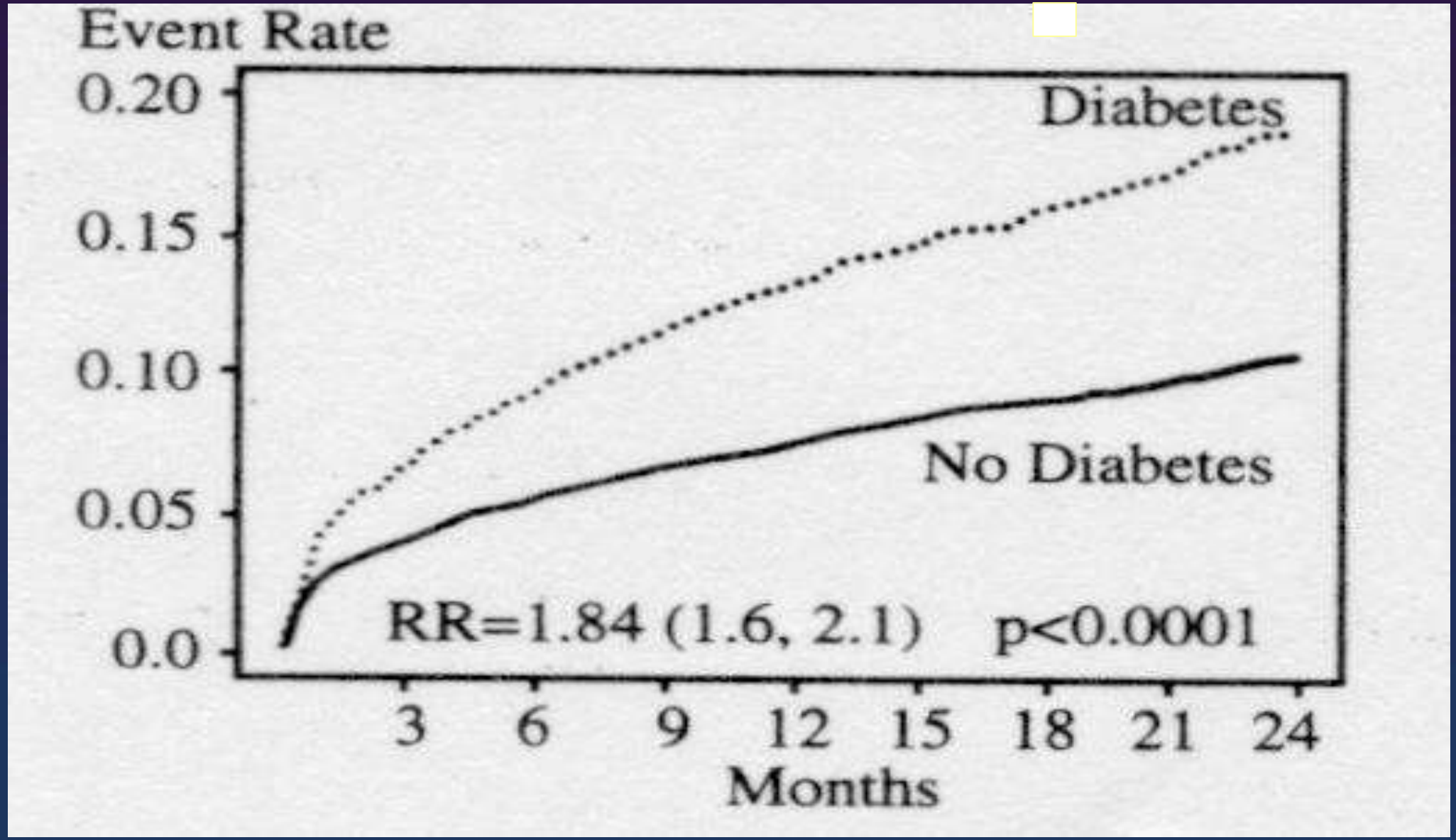
Diabetes: a Huge Problem in the US



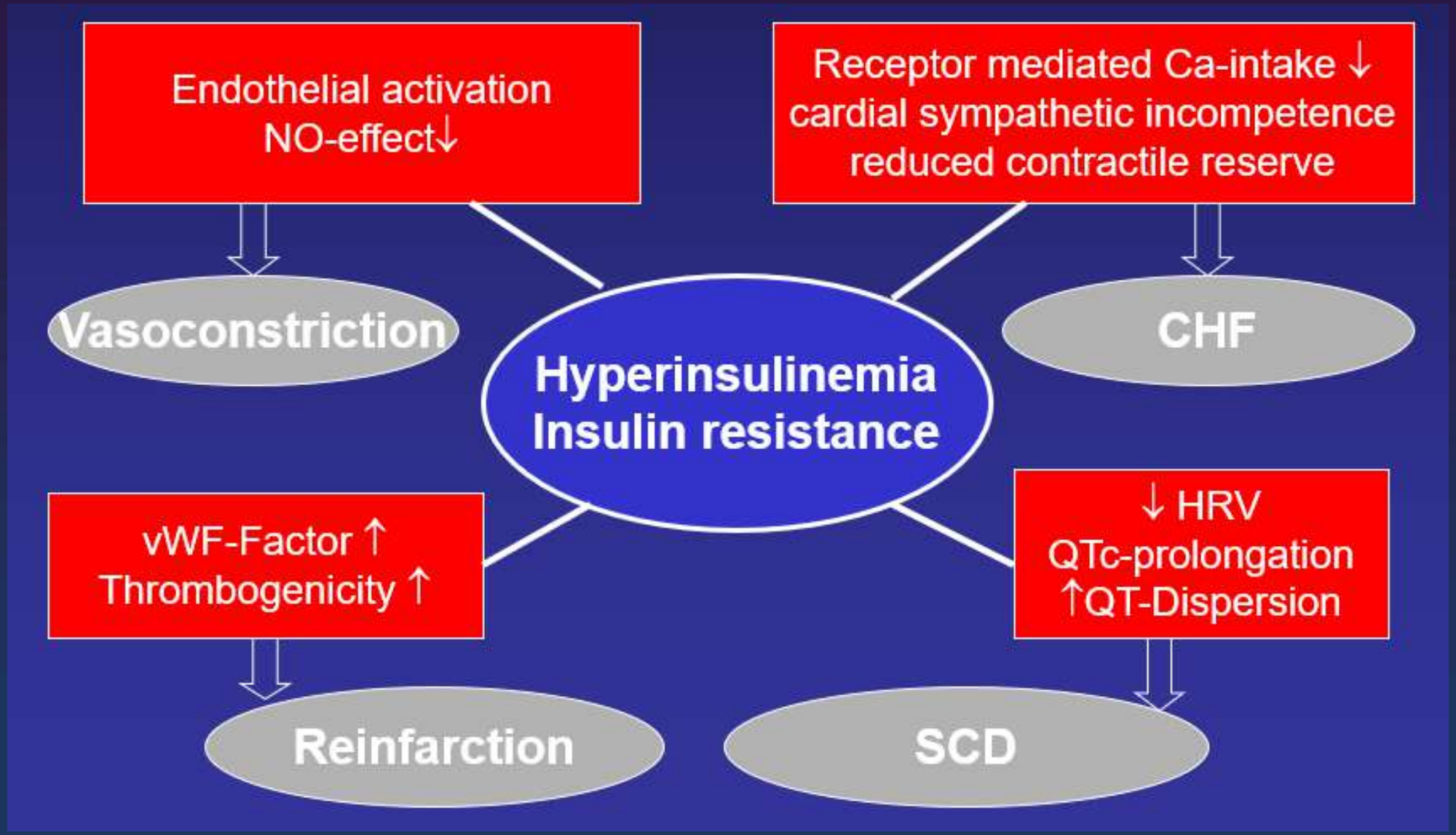
Kenny SJ .In: Diabetes in America, 2nd ed. 1995. Bethesda, MD: NIHo 1995

Mortality after MI in Diabetes

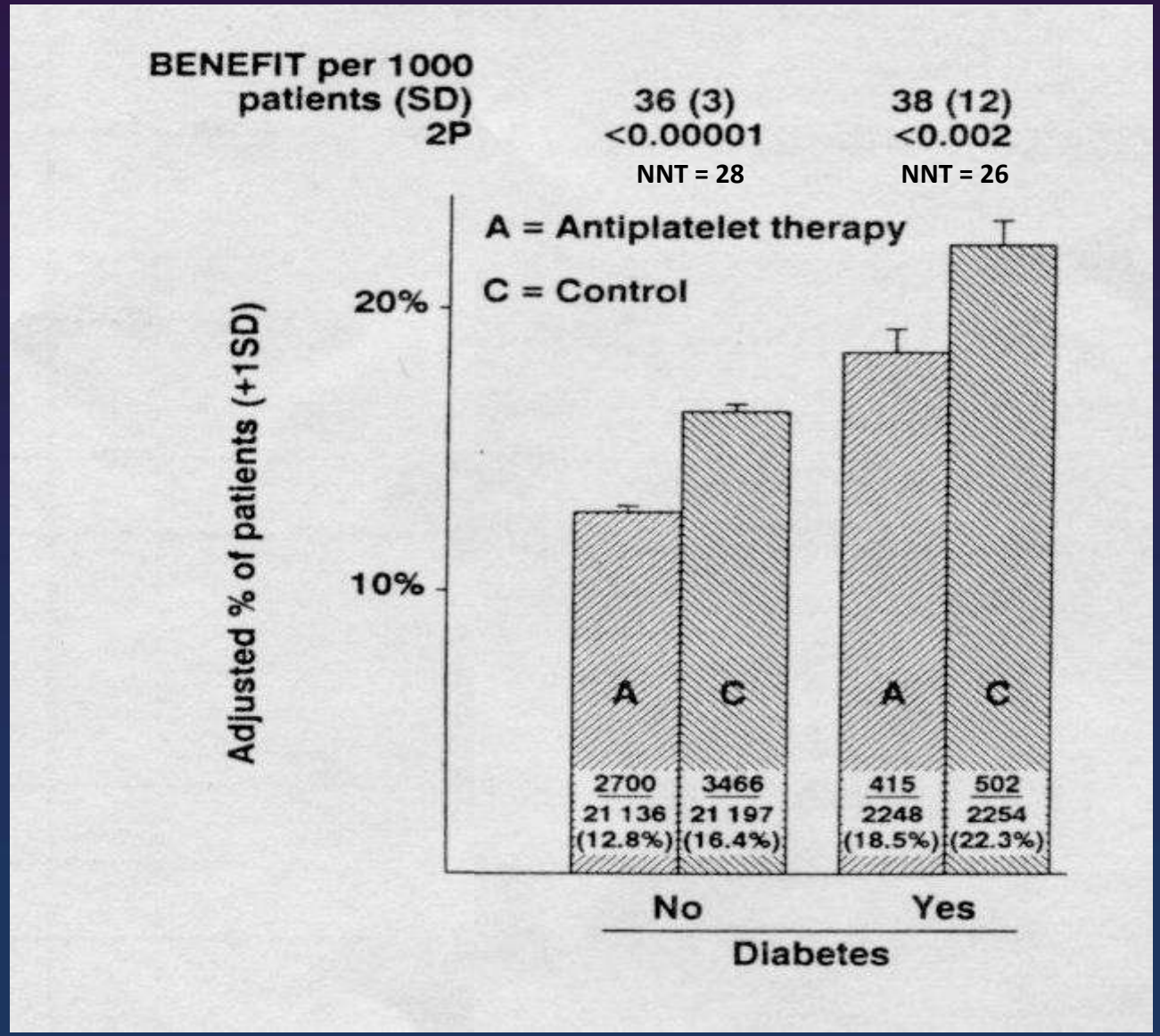


OASIS registry. Circulation 2000;102:1014-1919

Reason for Increased Morbidity and Mortality in Diabetes after MI



Aspirin after MI in Diabetes



Antiplatelet Trialists'Collaboration. BMJ 1994;308:71-106

Clopidogrel after MI in Diabetes

CURE

death/(re)MI/stroke at 12 months		placebo	clopidogrel	RR	p	
diabetics	(n=2,840)	16.7 %	14.2 %	0.85	0.07	p_{int} = NS
non-diabetics	(n=9,722)	9.9 %	7.9 %	0.80	0.001	

CURE. N Engl J Med 2001;345:494-502

Ticagrelor after ACS in Diabetes

European Heart Journal
doi:10.1093/eurheartj/ehq325

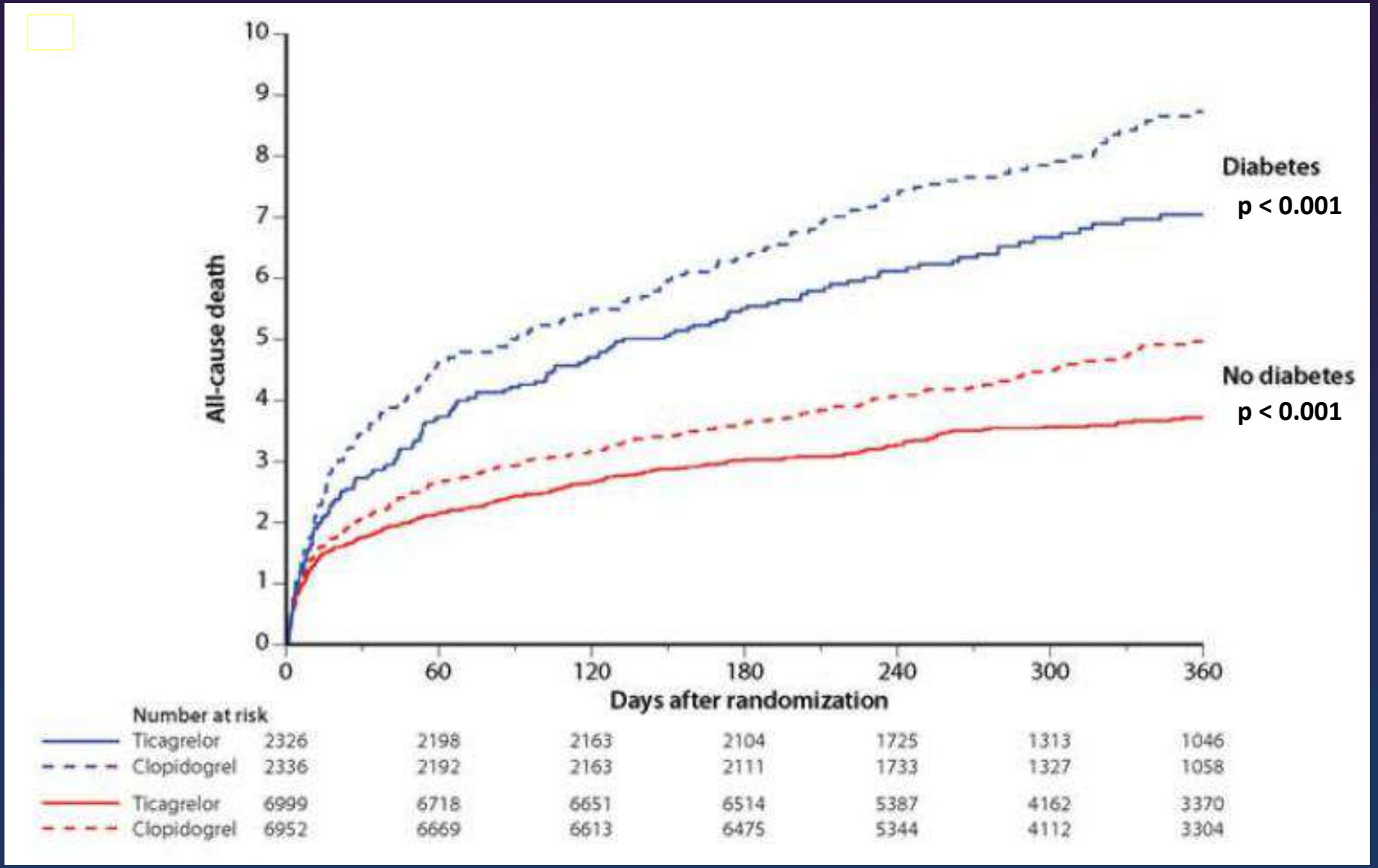
FASTTRACK
ESC CLINICAL TRIAL UPDATE

Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial

Stefan James[1]*, Dominick J. Angiolillo[2], Jan H. Cornel[3], David Erlinge[4], Steen Husted[5], Frederic Kontny[6], Juan Maya[7], Josë C. Nicolau[8], Jindrich Spinar[9], Robert F. Storey[10], Susanna R. Stevens[11], and Lars Wallentin[1], for the PLATO study group

Eur Heart J 2010;31:3006-3016

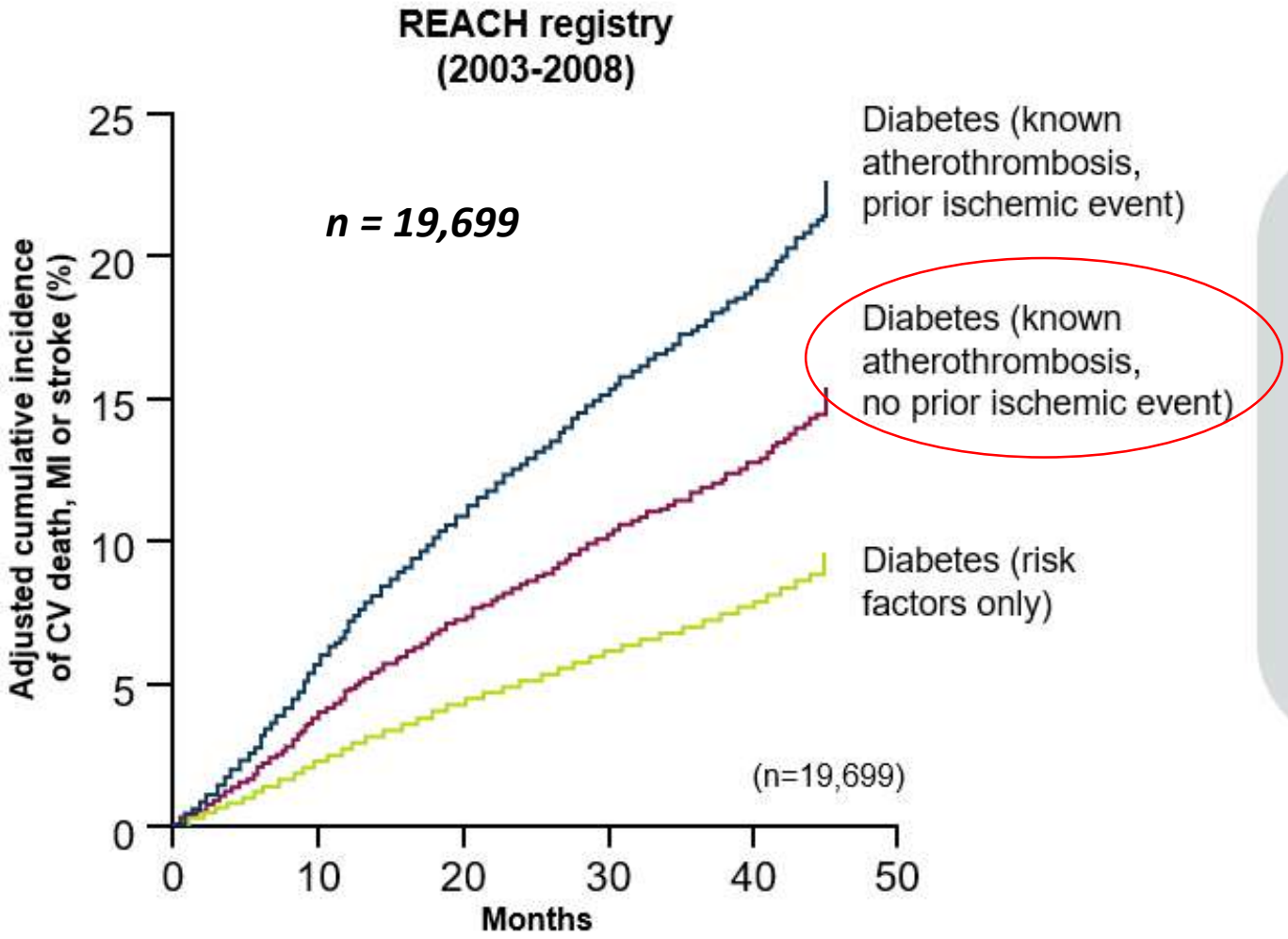
Mortality with Ticagrelor after MI in Diabetes



p int = 0.66

Eur Heart J 2010;31:3006-3016

Risk of Ischemic Events with and without Prior Event in Diabetics



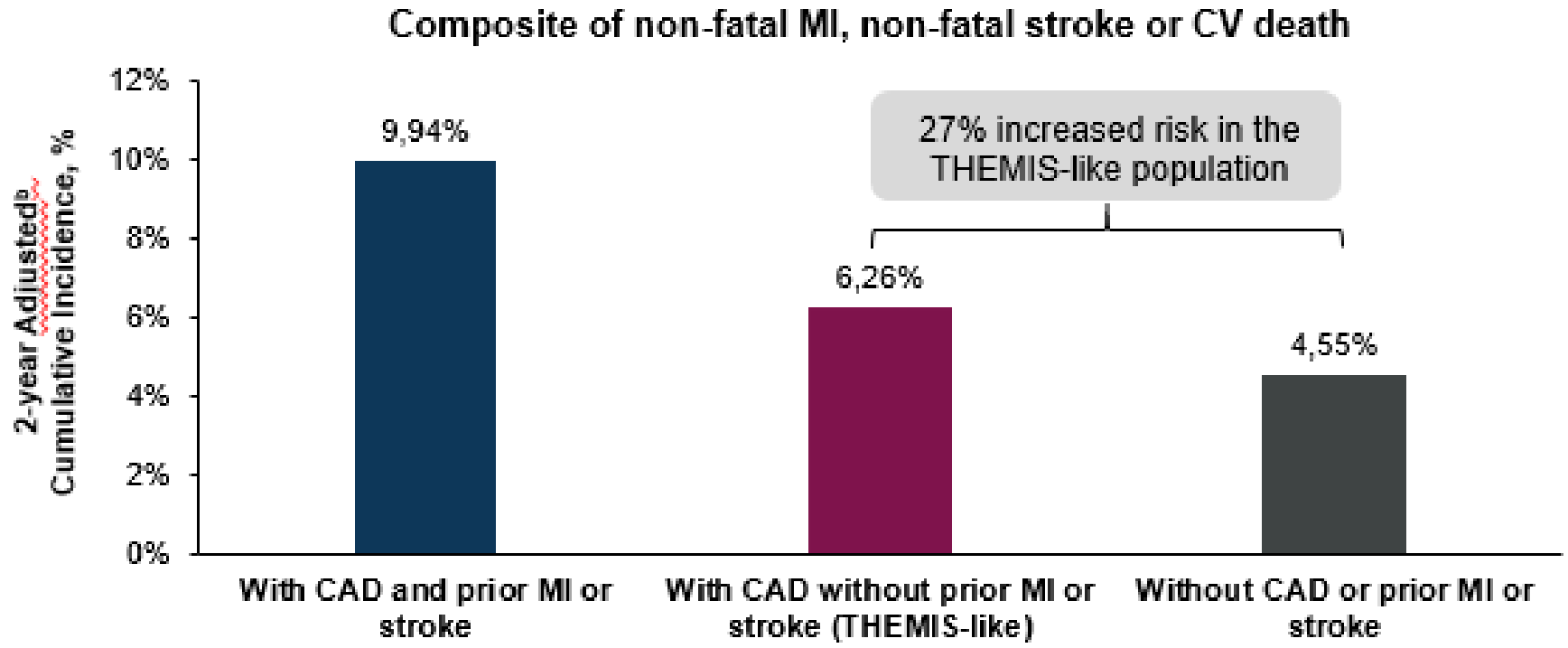
- Known atherothrombosis increased a patient's cumulative risk of MACE and could be further potentiated by a history of a prior ischemic event.
- 4-year hazard rates in patients with diabetes + known atherothrombosis + no prior MI:
  - CV death, MI or stroke: **14.8%** (95% CI, 13.3–16.2)
  - CV death: **7.7%** (95% CI, 6.6–8.8)
  - Non-fatal MI: **4.1%** (95% CI, 3.2–4.9)
  - Non-fatal stroke: **4.6%** (95% CI, 3.7–5.5)

Cavender MA. Circulation 2015;132:923–931

Available data from the ATHENA RWE program demonstrates an elevated risk for CV events in a "THEMIS-like" population

- ATHENA RWE program aims to utilize global real world databases and registries of patients with **type 2 diabetes and CAD** to describe the burden of illness in **THEMIS-like populations**[1]
- **ATHENA Sweden (DAISY registry)**[2]

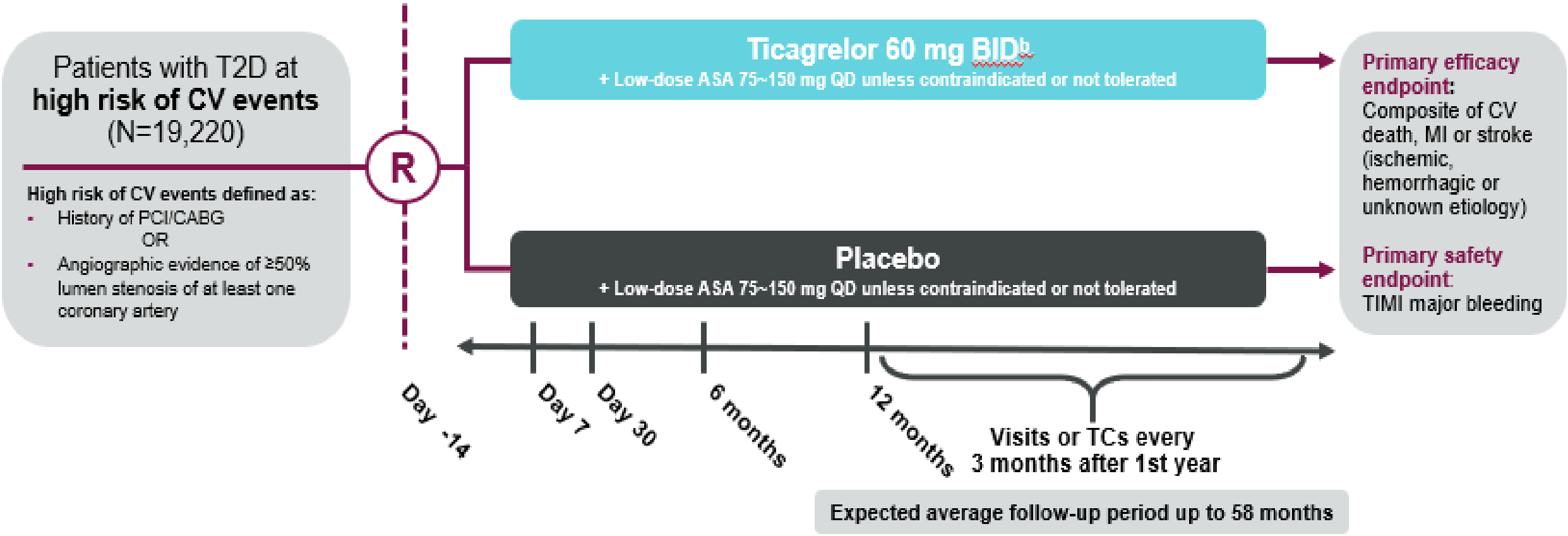
  N=332,170 patients with type 2 diabetes[a] identified through 3 nationwide registries



Jensberg T. Eur Heart J 2018;39(suppl 1):1355-1356. Abs P6425

THEMIS Trial: Design

- Phase 3b placebo-controlled event-driven RCT looking to collect 1385 primary efficacy events for an annual event rate of 2.5% in placebo group to provide a power of 90%
- Primary objective: compare ticagrelor BID vs placebo for the prevention of CV events in patients with T2D at high risk of CV events



Clin Cardiol 2019 ;42:498-505

THEMIS Trial: In- and Exclusion Criteria

Inclusion Criteria

- Men and women ≥ 50 years of age with **type 2 diabetes mellitus**
  - Treatment with a glucose lowering medication since at least 6 months prior to first visit

- **High risk of a CV event:**
  - Previous revascularization of a coronary artery (PCI/CABG)

  OR
  - Angiographic evidence of ≥50% lumen stenosis of at least one coronary artery

Exclusion Criteria

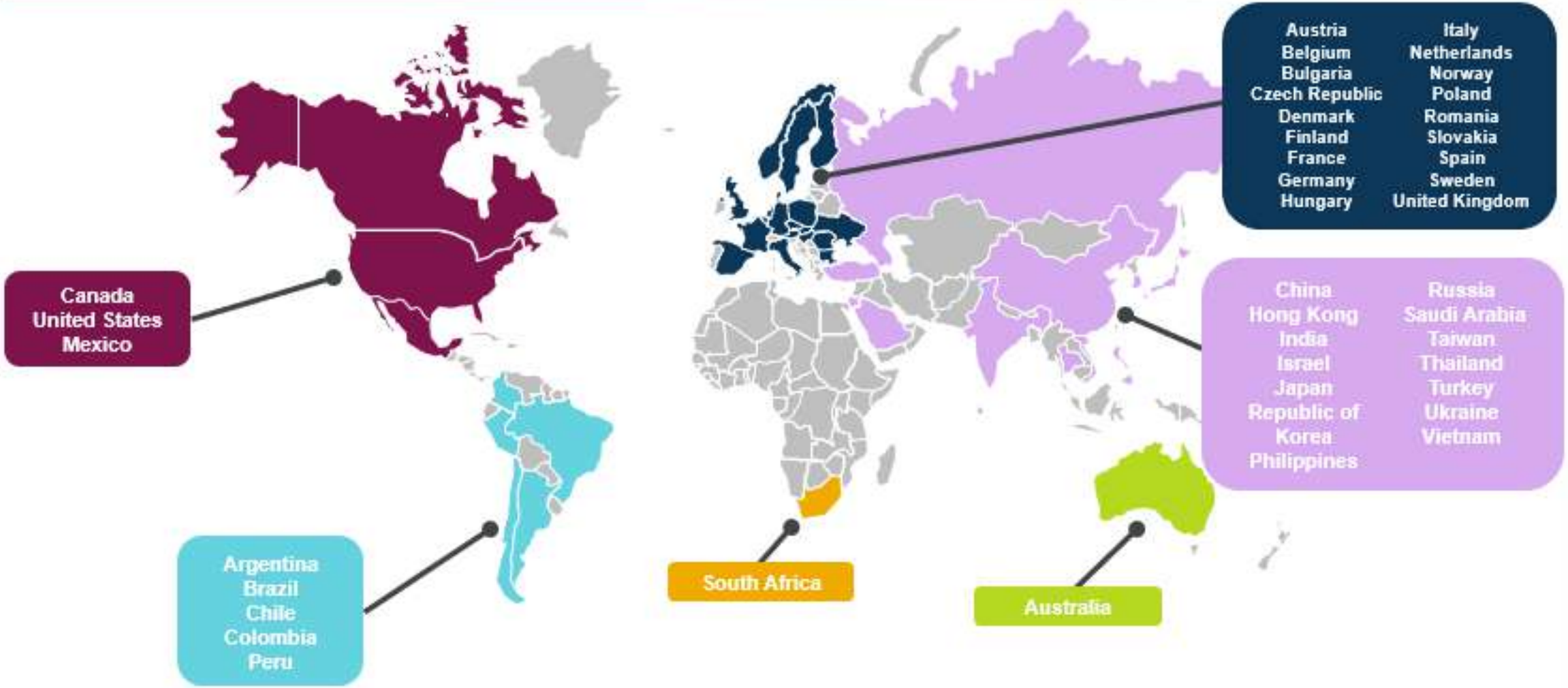
- **History of previous MI or stroke (excluding TIA)**
- Planned use of: ADP receptor antagonists, dipyridamole, cilostazol or ASA treatment at doses >150 mg daily
- Planned coronary, cerebrovascular, or peripheral artery revascularization

Additional Exclusion Criteria

- Concomitant use of strong CYP3A4 inhibitors or substrates with narrow therapeutic indices
- Need for chronic oral anticoagulant therapy or LMWH
- Known bleeding diathesis or coagulation disorder
- Uncontrolled hypertension (systolic BP ≥180 mm Hg and/or diastolic BP ≥100 mm Hg)
- History of previous intracranial bleed at any time, GI bleed within 6 months prior to randomization, or major surgery within 30 days prior to randomization
- Increased risk of bradycardic events unless treated with a pacemaker
- Known severe liver disease or renal failure requiring dialysis

THEMIS Trial: Participating Countries

Global Participation



THEMIS Trial: Baseline Characteristics

Characteristic[a]	Randomized patients (N=19,220)
Age (years) - median [IQR]	66.0 (61.0-72.0)
Male	13,189 (68.6)
BMI (kg/m²) - median [IQR]	29.0 (26.0-32.7)
Current smoker	2094 (10.9)
Race	
Asian	4406 (22.9)
Black or African American	403 (2.1)
Other	715 (3.7)
White	13,696 (71.3)
Geographic region	
Asia and Australia	4288 (22.3)
Central and South America	2169 (11.3)
Europe, Middle East, and South Africa	9768 (50.8)
North America	2995 (15.6)
Medication use at baseline[b]	
Aspirin	19,104 (99.4)
Aspirin dose (mg)- median [IQR]	100 (80-100)
Statin	17,266 (89.8)
Proton pump inhibitor	4901 (25.5)
ACE-inhibitor or ARB	15,113 (78.6)
Beta blocker	14,192 (73.8)
Insulin	5508 (28.7)
Any diabetes medications	19,156 (99.7)
1	8609 (44.8)
2	6911 (36.0)
3	2892 (15.0)
>3	744 (3.9)

THEMIS Trial: Disease History

Disease history[a]	Randomized patients (N=19,220)
Hypertension	17,776 (92.5)
Dyslipidemia	16,753 (87.2)
History of angina pectoris	10,801 (56.2)
Multi-vessel coronary artery disease (>1 vessel)	11,935 (62.1)
Revascularization status	
Previous PCI only	9808 (51.0)
Previous CABG only	4191 (21.8)
Previous PCI and CABG	1346 (7.0)
No previous revascularization[b]	3875 (20.2)
Time since most recent PCI (years), median [IQR]	3.3 (1.5-6.6)
Time since most recent CABG (years), median [IQR]	4.3 (1.5-9.2)
History of peripheral artery disease	1687 (8.8)
History of poly-vascular disease[c]	2579 (13.4)
Duration of diabetes (years), median [IQR]	10.0 (5.0-16.0)
History of any diabetes complications[d]	4910 (25.5)
HbA1c at baseline (%), median [IQR]	7.1 (6.4-8.1)
eGFR (MDRD) at baseline (mL/min/1.73 m^2), median [IQR]	75.0 (60.5-89.6)

THEMIS Trial: Press Release February 25, 2019

- The Phase III THEMIS trial met its primary endpoint which demonstrated that ticagrelor, taken in conjunction with ASA, showed a statistically-significant reduction in a composite of major adverse cardiovascular events (MACE) compared to ASA alone.
- Preliminary safety results were consistent with the known profile of ticagrelor.
- A full evaluation of the THEMIS data will be presented at a forthcoming medical meeting.

THEMIS Trial Presentation: Hotline 1 on Sunday Sep 1, 2019 at 14.30-15.40h at ESC, Paris

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Conclusions

1. Diabetes mellitus doubles the risk of mortality after MI
2. In diabetes antiplatelet therapy with aspirin reduces the risk of recurrent MI and stroke significantly
3. On top of aspirin ticagrelor but not clopidogrel reduces the mortality risk further
4. Diabetic patients with proven athersthrombosis but without a history of an ischemic event double their risk of a future event in comparison with diabetic patients without atherothrombosis
5. In such patients the THEMIS trial has studied the role of ticagrelor plus aspirin vs aspirin alone in the prevention of ischemic outcomes, apparently with a positive result