

# Disclosures

Il prof. **Domenico Tricò** dichiara di aver ricevuto compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

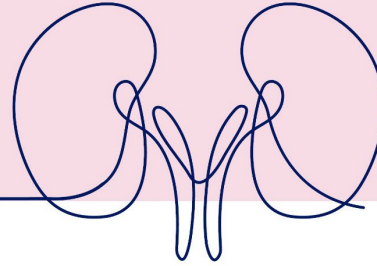
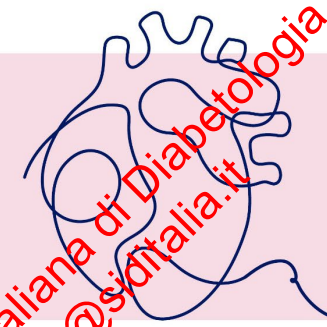
- AstraZeneca
- Boehringer Ingelheim
- Eli Lilly
- Novo Nordisk
- Vertex

*Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).*

Diapositiva preparata da DOMENICO TRICO' e ceduta alla Società Italiana di Diabetologia.  
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Diagnosi precoce e  
trattamento efficace  
della patologia

**CARDIONEFRO  
METABOLICA**



# Legacy effect: glicemico o multifattoriale?

**Domenico Tricò**

Professore Associato in Medicina Interna

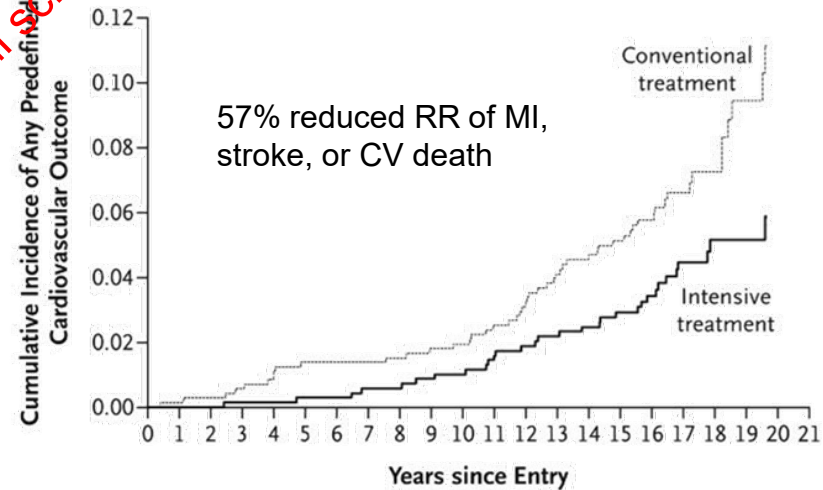
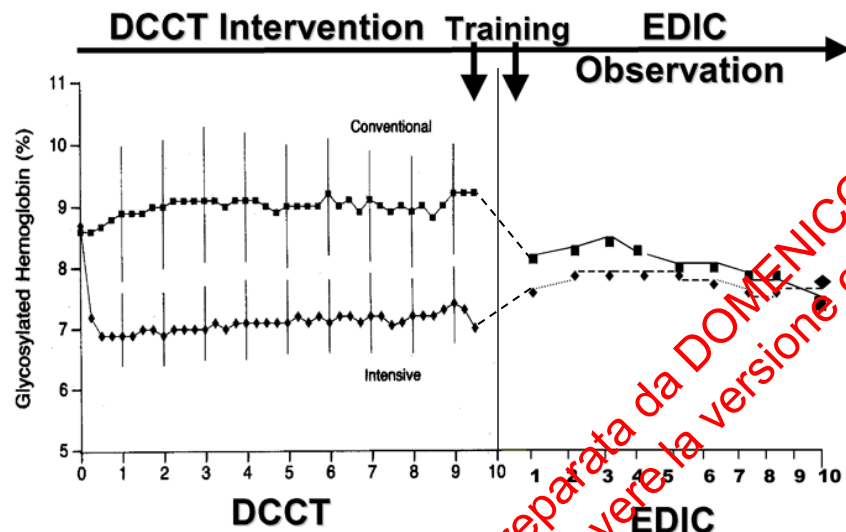
Dipartimento di Medicina Clinica e Sperimentale

Università di Pisa

Napoli, 21 Novembre 2025

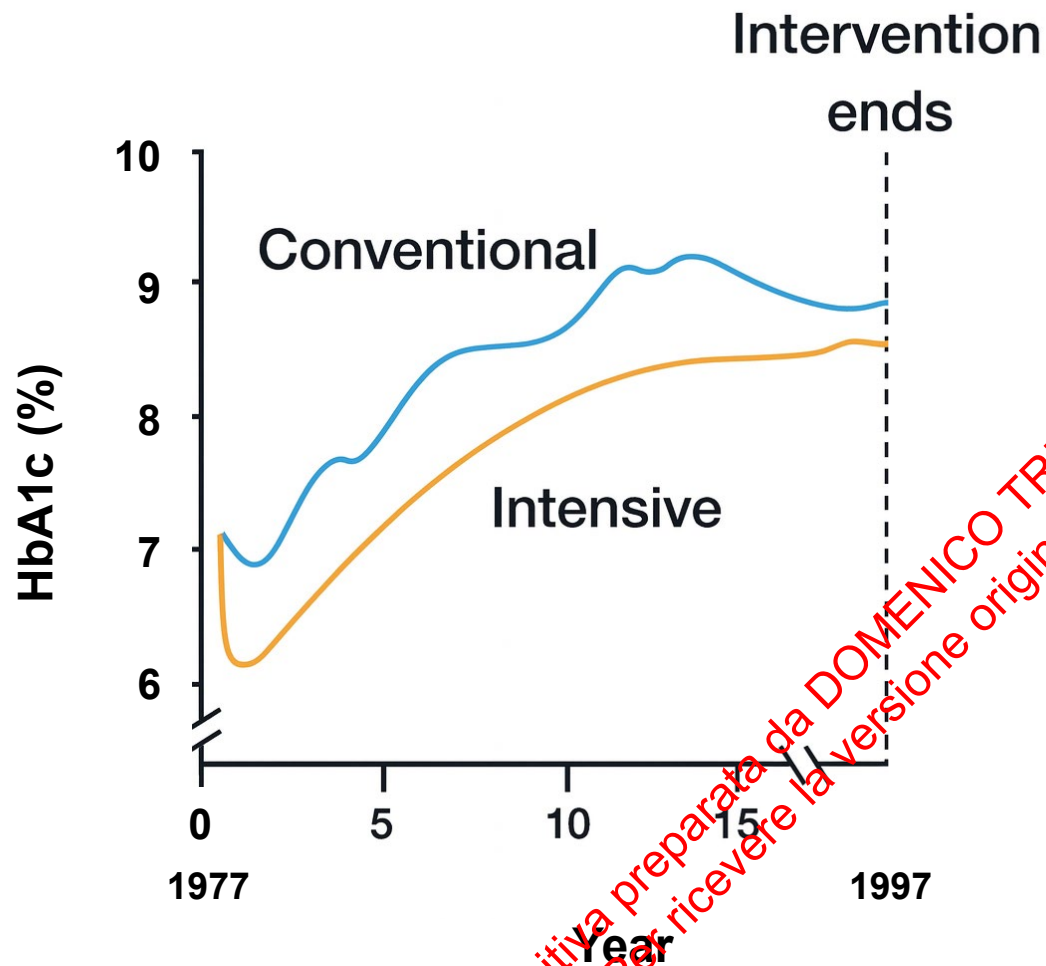
# Legacy effect: Definition

A phenomenon of continuous beneficial effect of the intensive control on disease outcomes or complications even after a long duration of cessation of the intervention.



| No. at Risk            |     |     |     |     |
|------------------------|-----|-----|-----|-----|
| Intensive treatment    | 705 | 683 | 629 | 113 |
| Conventional treatment | 714 | 688 | 618 | 92  |

# Legacy effect of intensive glycemic control: UKPDS

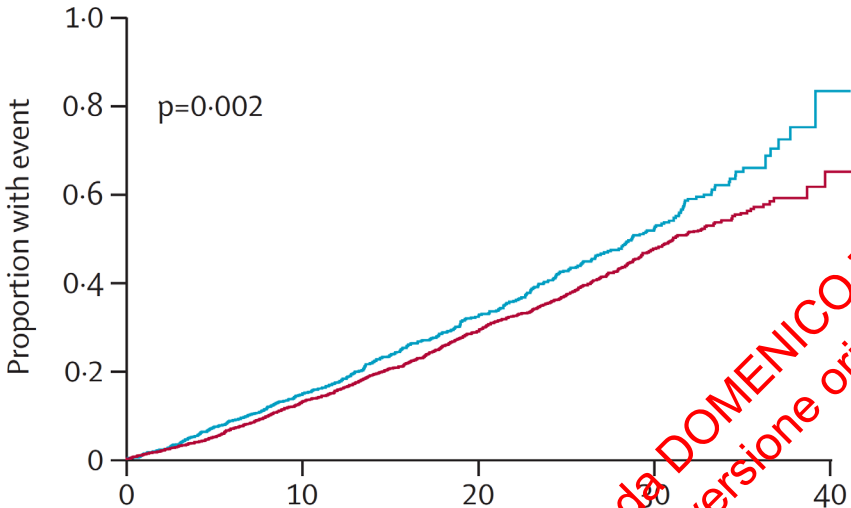


After the intervention, RR reduction in:

- **Microvascular complications** 25% (7-40%)
- **MI** 16% (29-0%)  $p=0.052$
- **All-cause mortality** *ns*

# Legacy effect of intensive glycemic control: UKPDS

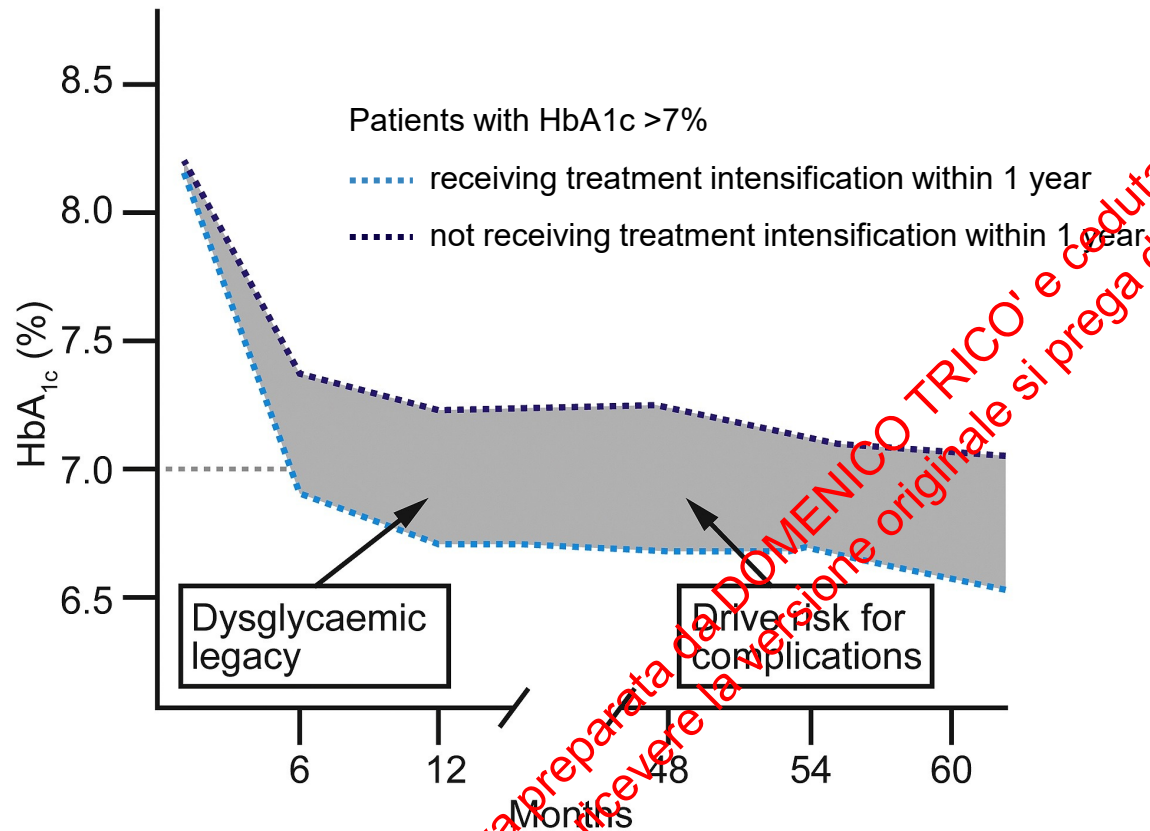
## Myocardial infaction



### RR reduction with intensive glucose control using suphonylurea/insulin

|                               | 1997 | 2007 | 2021 |
|-------------------------------|------|------|------|
| Any diabetes-related endpoint | 12%  | 9%   | 10%  |
| Myocardial infarction         | 16%  | 15%  | 17%  |
| Microvascular disease         | 25%  | 24%  | 26%  |
| All-cause mortality           | 6%   | 13%  | 10%  |

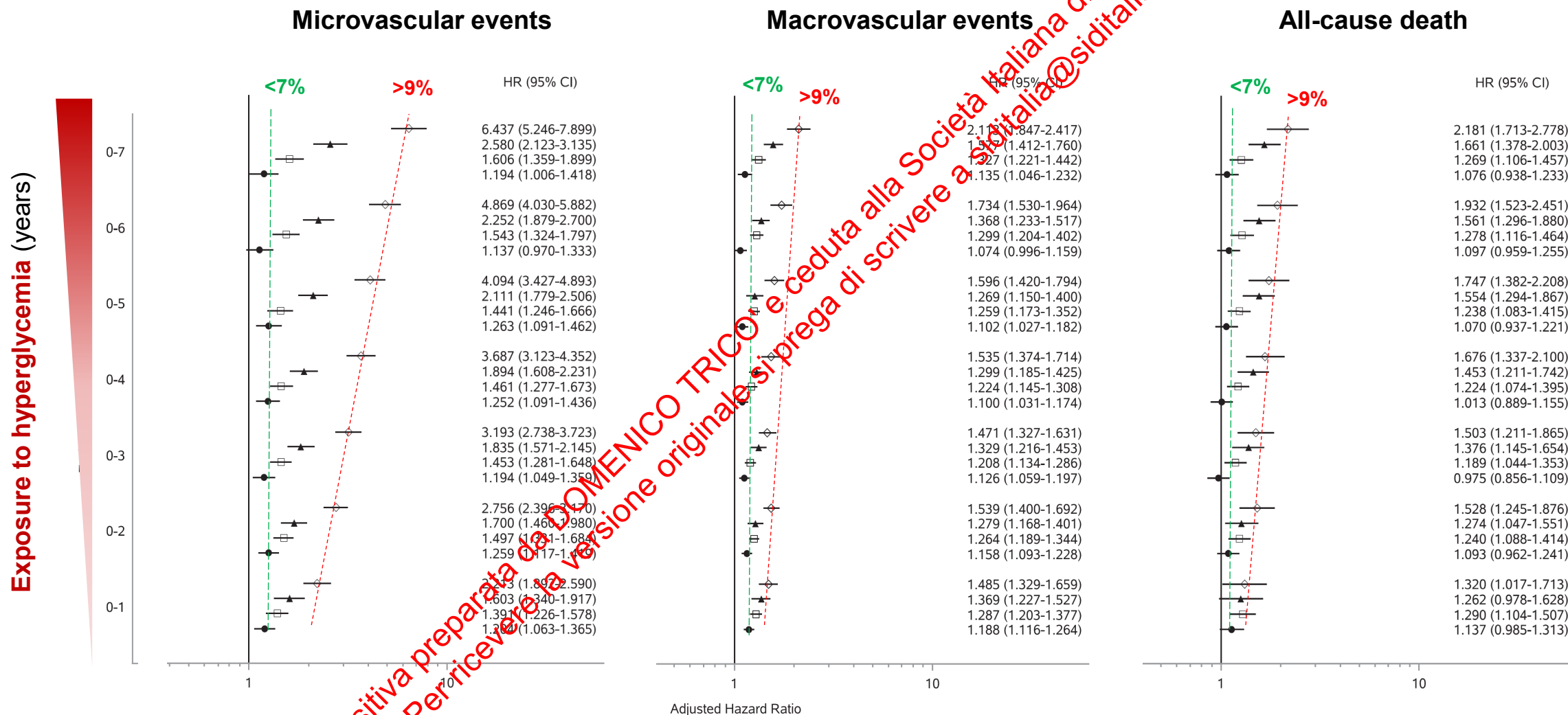
# Legacy effect of dysglycemia: UK CPRD



At 5.3 years, significantly increased risk of:

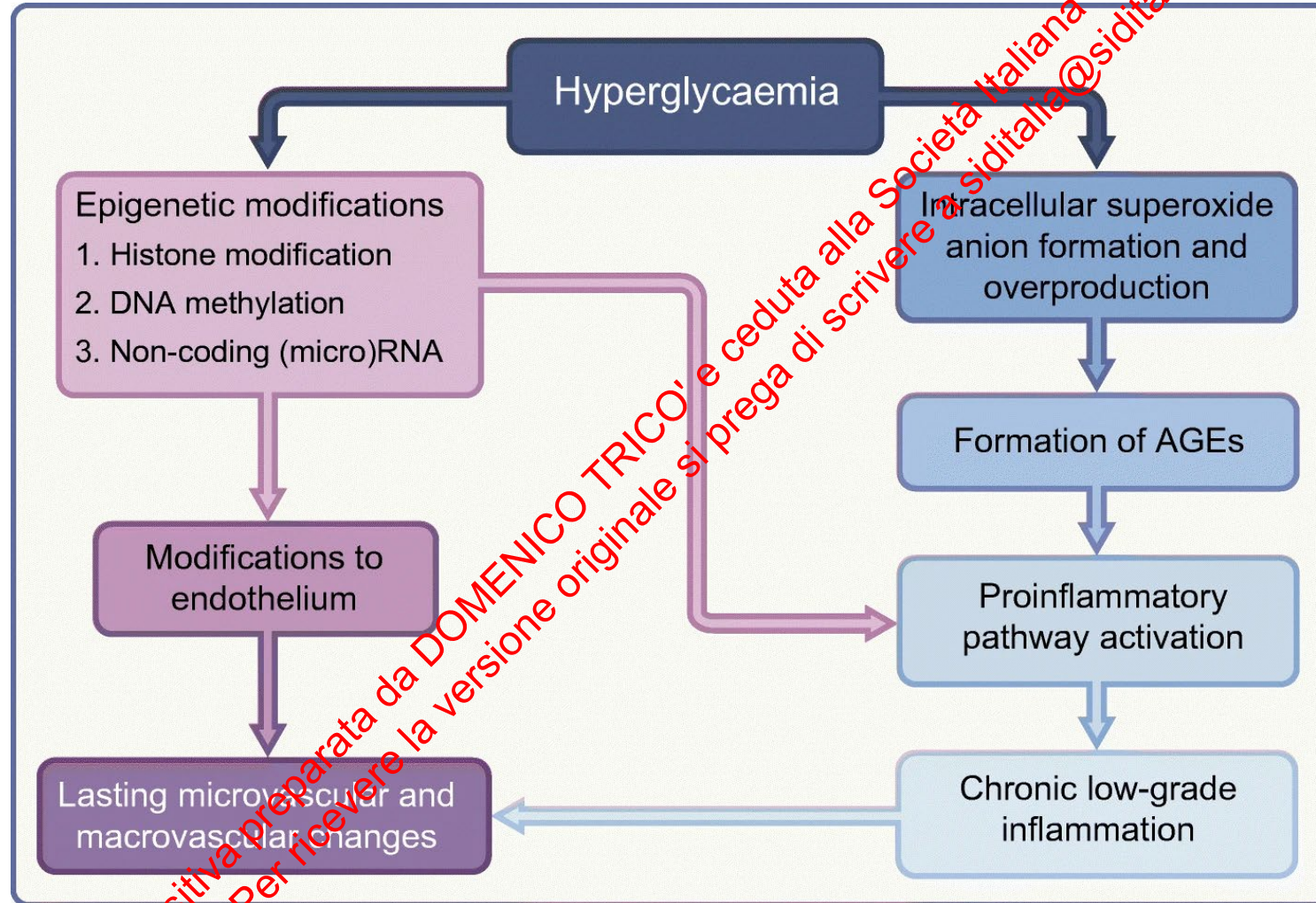
- **MI** 67% (39-101%)
- **Stroke** 51% (25-83%)
- **HF** 64% (40-91%)
- **Composite CV events** 62% (46-80%)

# Legacy effect of dysglycemia: Diabetes & Aging Study



- HbA1c 6.5% to <7.0% (48 to <53 mmol/mol)
- ▲ HbA1c 8.0% to <9.0% (64 to <75 mmol/mol)
- ◻ HbA1c 7.0% to <8.0% (53 to <64 mmol/mol)
- ◊ HbA1c >9.0% (>75 mmol/mol)

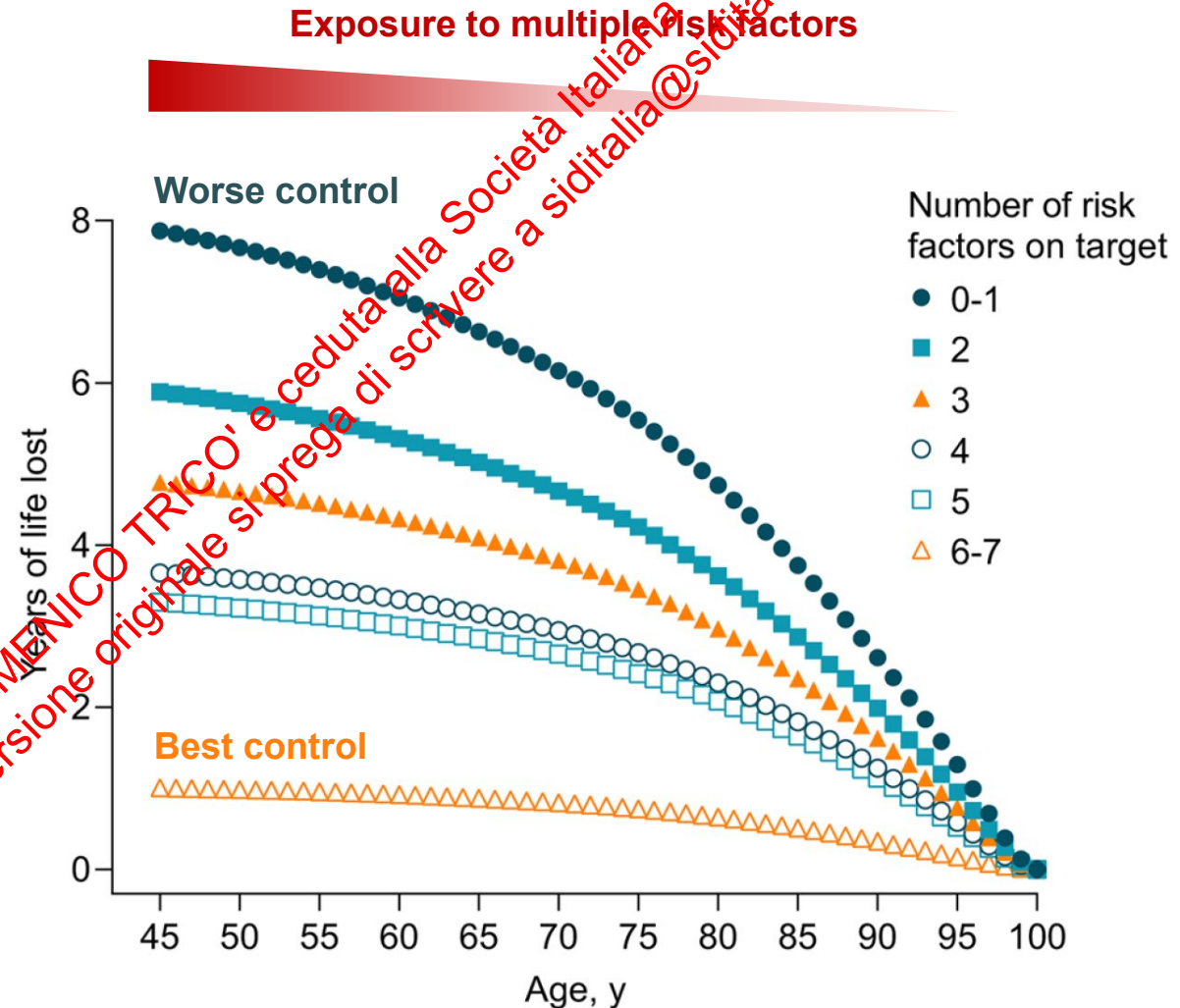
# Mechanisms of the legacy effect of glycemic control



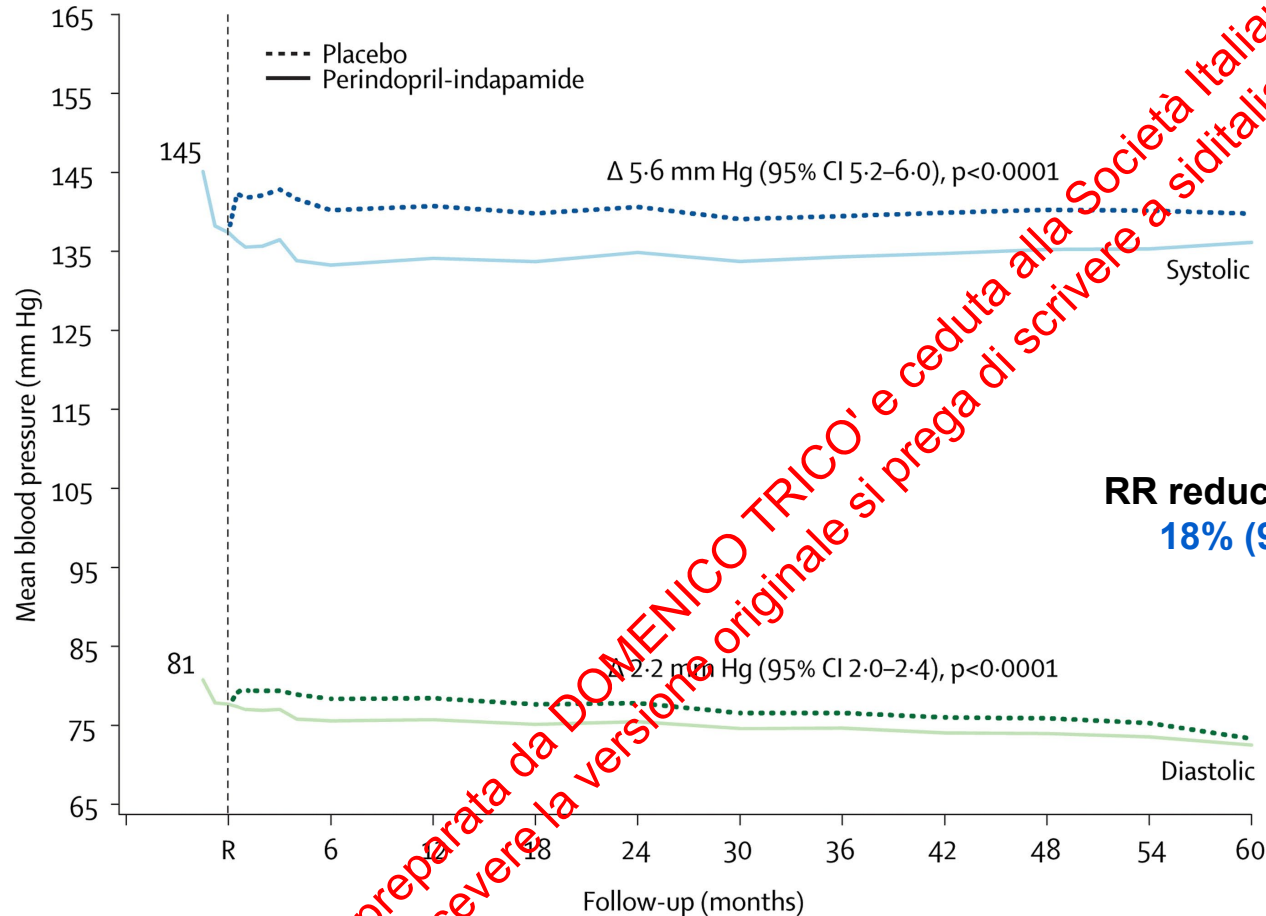
# Risk factors and mortality in type 2 diabetes

## Traditional risk factors:

- High glucose
- Arterial hypertension
- High cholesterol
- Overweight
- Physical inactivity
- Unhealthy diet
- Smoking



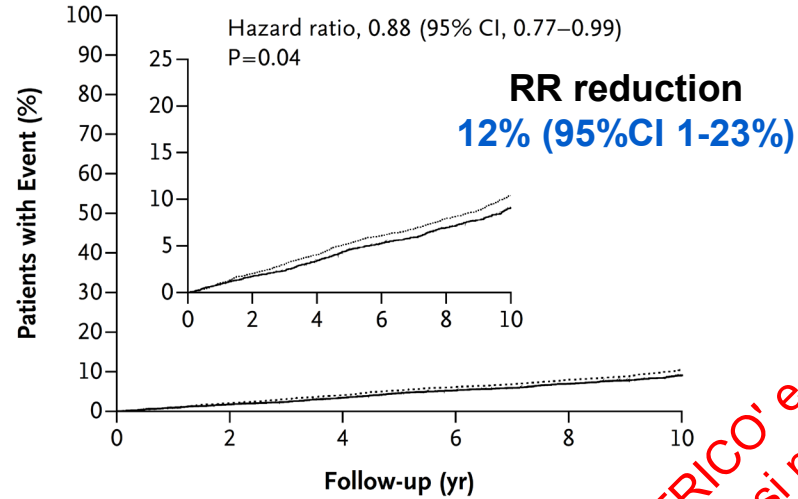
# Legacy effect of intensive blood pressure control: ADVANCE



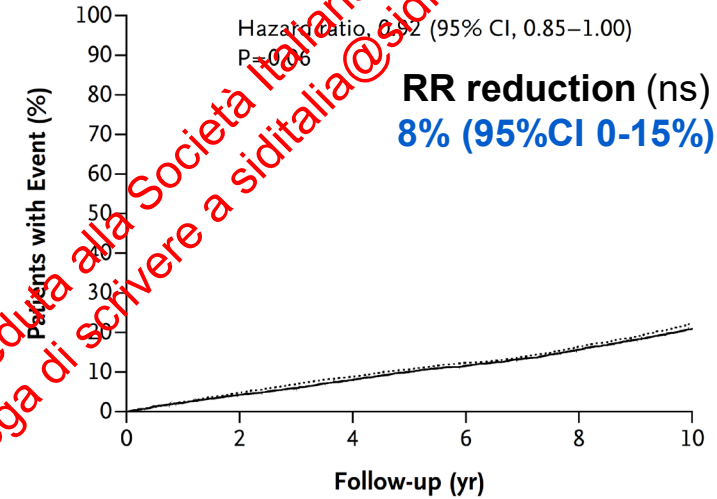
|         |        |        |        |        |        |        |        |        |        |        |        |
|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Placebo | 137/78 | 140/78 | 141/78 | 140/78 | 141/78 | 139/77 | 139/77 | 140/76 | 140/76 | 140/75 | 140/73 |
| Per-ind | 137/78 | 133/76 | 134/76 | 134/75 | 135/75 | 134/75 | 134/75 | 135/74 | 135/74 | 135/74 | 136/73 |

# Legacy effect of intensive blood pressure control: ADVANCE

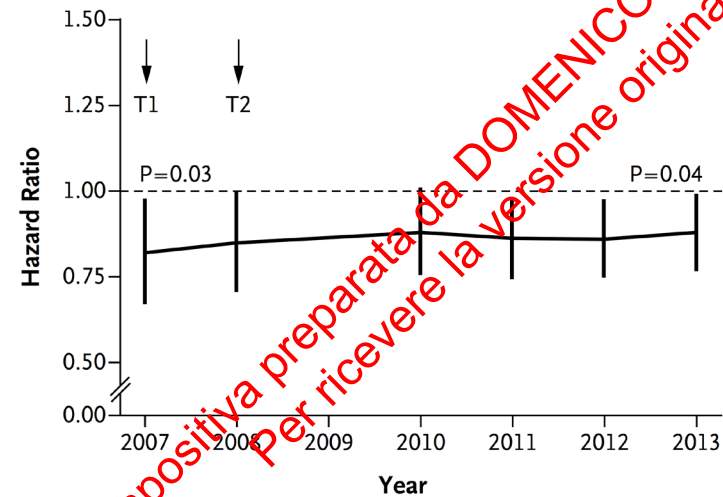
Death from Cardiovascular Causes



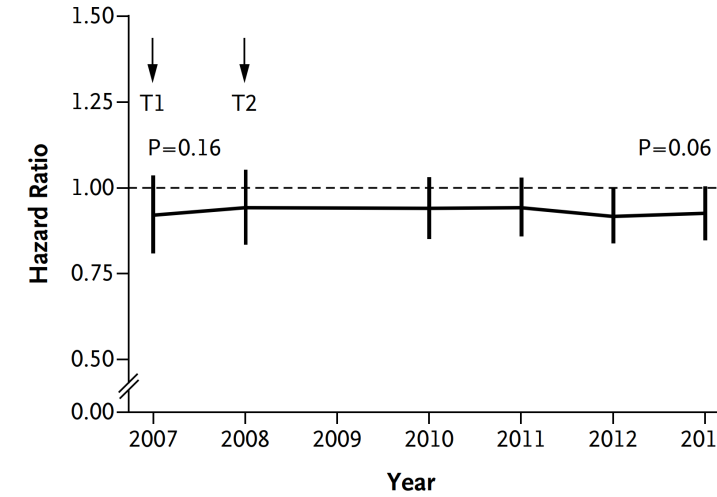
Major Macrovascular Events



Death from Cardiovascular Causes

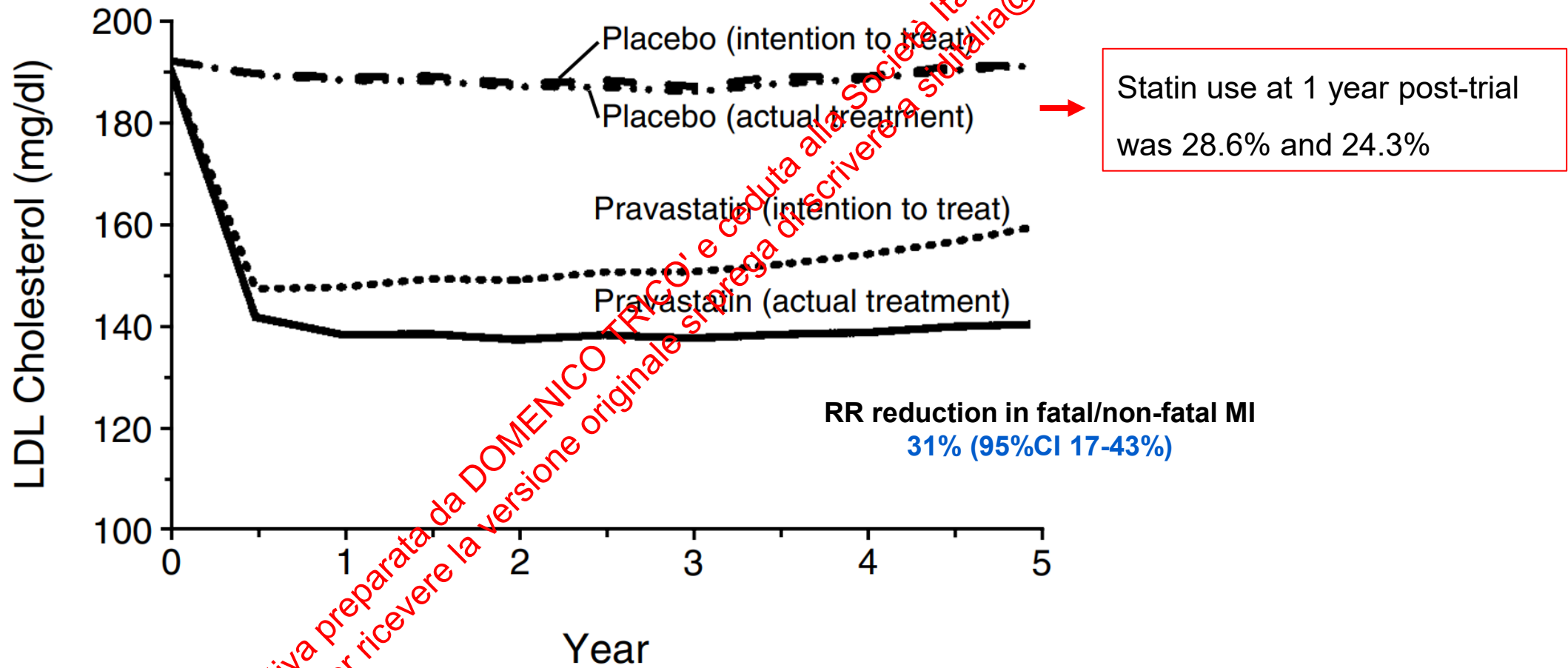


Major Macrovascular Events



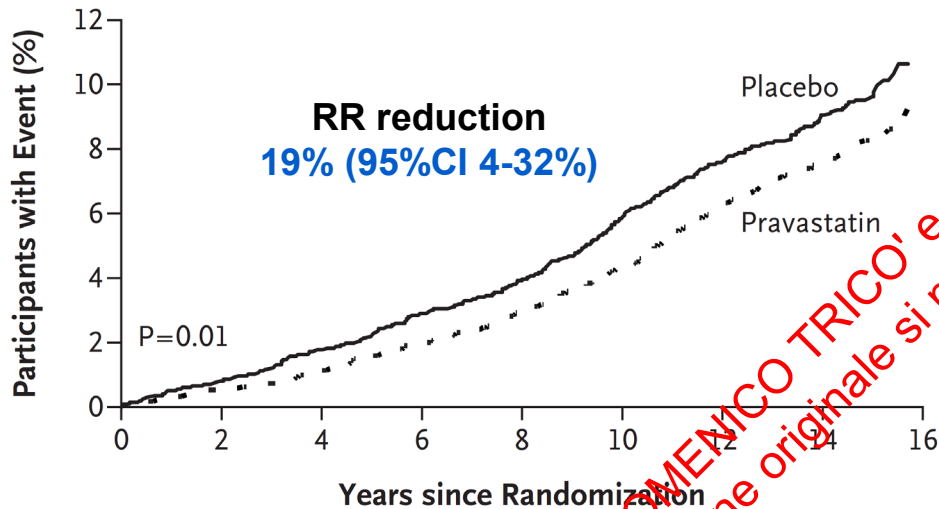
---- Placebo  
— Perindopril-indapamide

# Legacy effect of intensive cholesterol control: WOSCOPS



# Legacy effect of intensive cholesterol control: WOSCOPS

Death from Cardiovascular Causes



No. at Risk

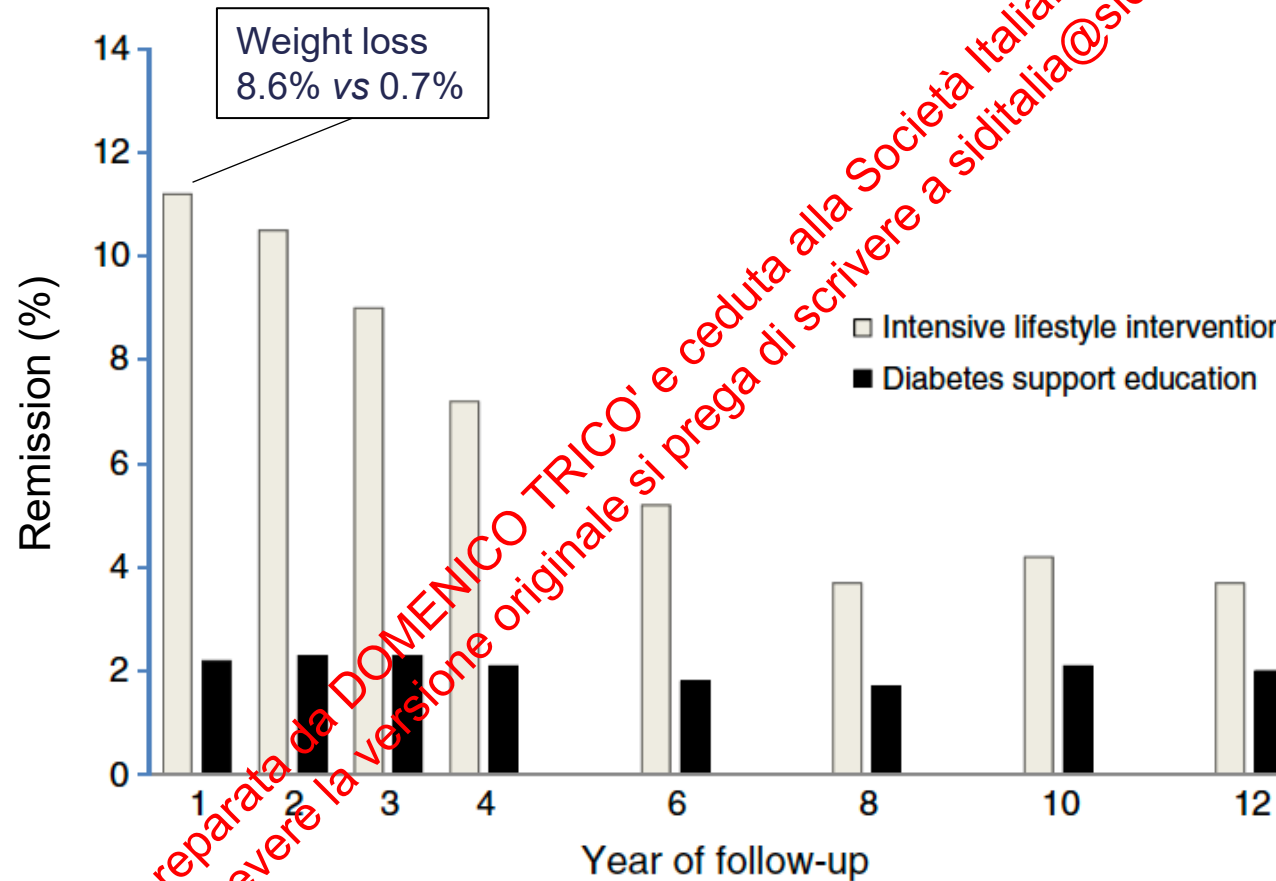
|             |      |      |      |      |      |      |      |      |
|-------------|------|------|------|------|------|------|------|------|
| Placebo     | 3293 | 3254 | 3185 | 3113 | 3022 | 2908 | 2785 | 2114 |
| Pravastatin | 3302 | 3275 | 3223 | 3158 | 3068 | 2974 | 2835 | 2177 |

RR reduction with intensive cholesterol control using pravastatin 40 mg

|                       | 1995 | 2004 |
|-----------------------|------|------|
| All-cause death       | 24%  | 12%  |
| CV death              | 34%  | 19%  |
| Fatal/nonfatal MI     | 40%  | 17%  |
| Fatal/nonfatal stroke | 33%  | 17%  |

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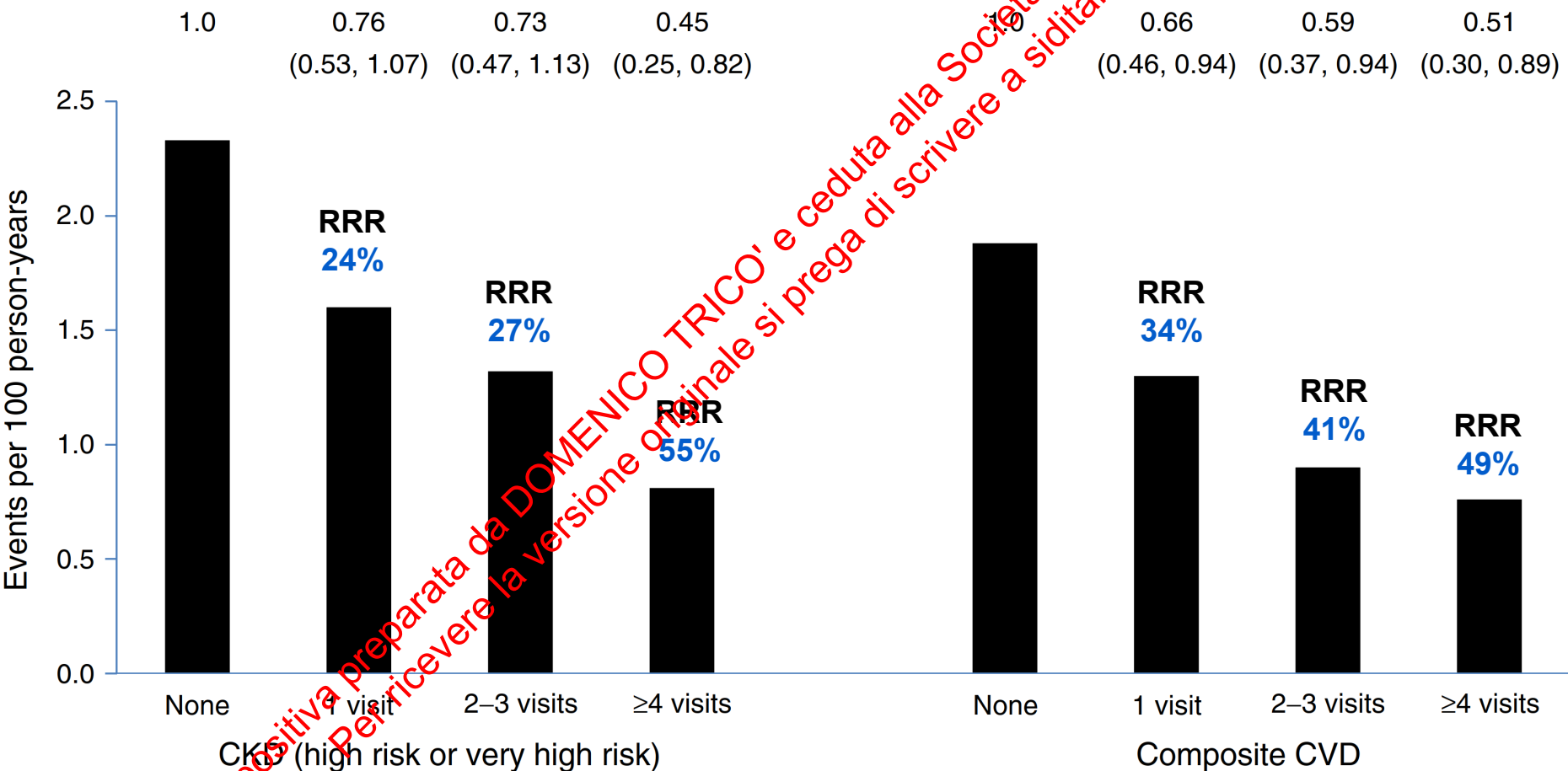
# Legacy effect of intensive body weight control: Look-AHEAD



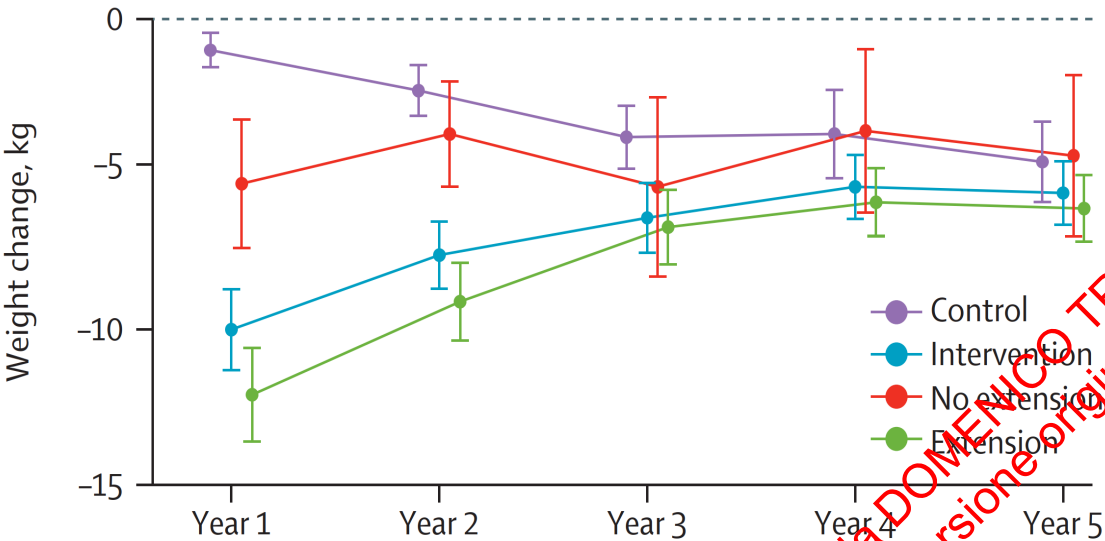
**Intensive intervention:** Low-calorie diet (1200-1800 kcal/die) with 1-2 meal replacements and >175 min/week moderate physical activity. Weekly visits for 6 months, then fortnightly visits up to 4 years.

# Legacy effect of intensive body weight control: Look-AHEAD

Incidence of CKD and CV events by number of visits with remission



# Legacy effect of intensive body weight control: DIRECT



MMACE \*

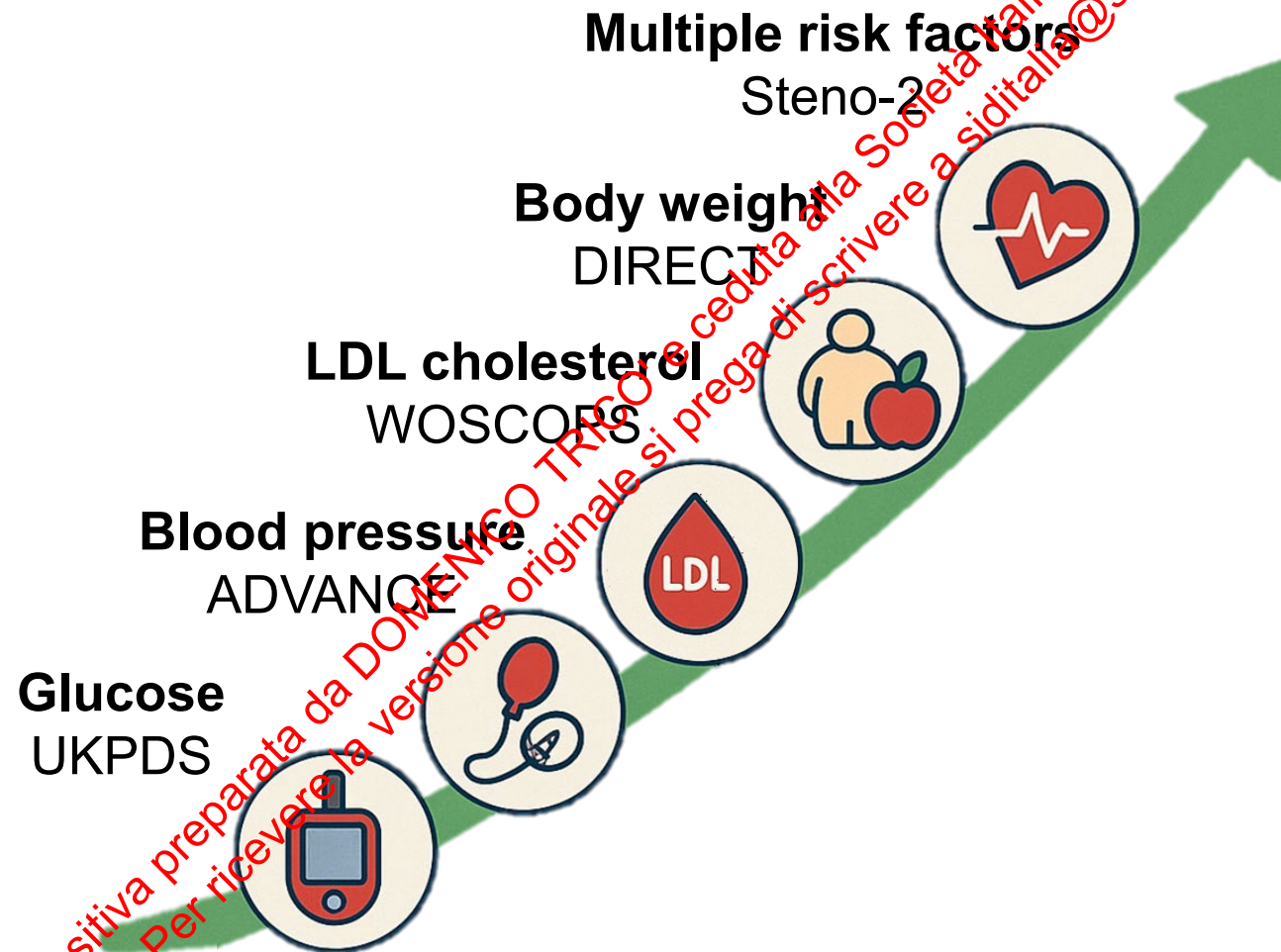
MADE \*\*

| Intervention, by Weight Loss at T1 |                   |               |     |                   |               |                                       |
|------------------------------------|-------------------|---------------|-----|-------------------|---------------|---------------------------------------|
| ≤5%                                |                   |               | >5% |                   |               | Est (CI), p-value                     |
| N                                  | Events (After T1) | Rate (/100py) | N   | Events (After T1) | Rate (/100py) |                                       |
| 33                                 | 4                 | 3.3           | 103 | 16                | 3.9           | 1.2 (0.4, 3.6), p=0.74 <sup>P</sup>   |
| 47                                 | 6                 | 4.3           | 79  | 8                 | 3.4           | 0.8 (0.3, 2.3), p=0.67 <sup>P</sup>   |
| 55                                 | 6                 | 5.5           | 63  | 3                 | 2.4           | 0.4 (0.1, 1.8), p=0.25 <sup>P</sup>   |
| 50                                 | 4                 | 8.0           | 62  | 1                 | 1.6           | 0.2 (0.0, 1.8), p=0.15 <sup>P</sup>   |
| 33                                 | 28                | 23.0          | 103 | 52                | 12.8          | 0.6 (0.3, 0.9), p=0.031 <sup>NB</sup> |
| 47                                 | 28                | 20.1          | 79  | 29                | 12.4          | 0.6 (0.4, 1.0), p=0.067 <sup>P</sup>  |
| 55                                 | 25                | 22.7          | 63  | 16                | 12.8          | 0.6 (0.3, 1.1), p=0.073 <sup>P</sup>  |
| 50                                 | 12                | 24.0          | 62  | 5                 | 8.1           | 0.3 (0.1, 1.0), p=0.040 <sup>P</sup>  |

\* Moderate/Major Adverse CV Events: CV death, MI, stroke/TIA, HF, unstable angina, PAD

\*\* Moderate/Major Adverse Diabetes Events: MMACE + severe hypoglycemia, DKA, retinopathy, CKD, foot disease

# Legacy effect of intensive multiple risk factor control



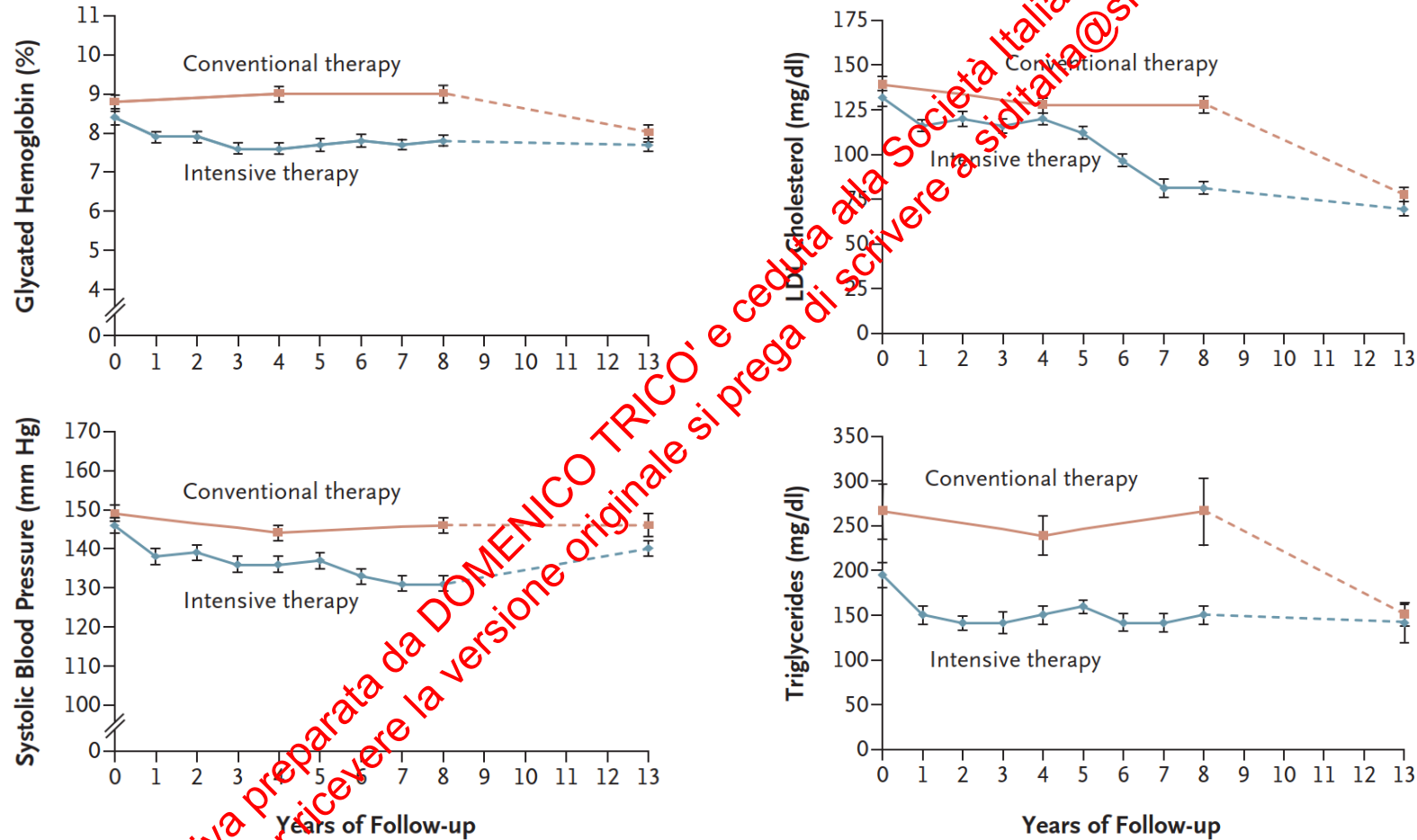
# Legacy effect of intensive multiple risk factor control: Steno-2

**Table 1. Treatment Goals for the Conventional-Therapy Group and the Intensive-Therapy Group.\***

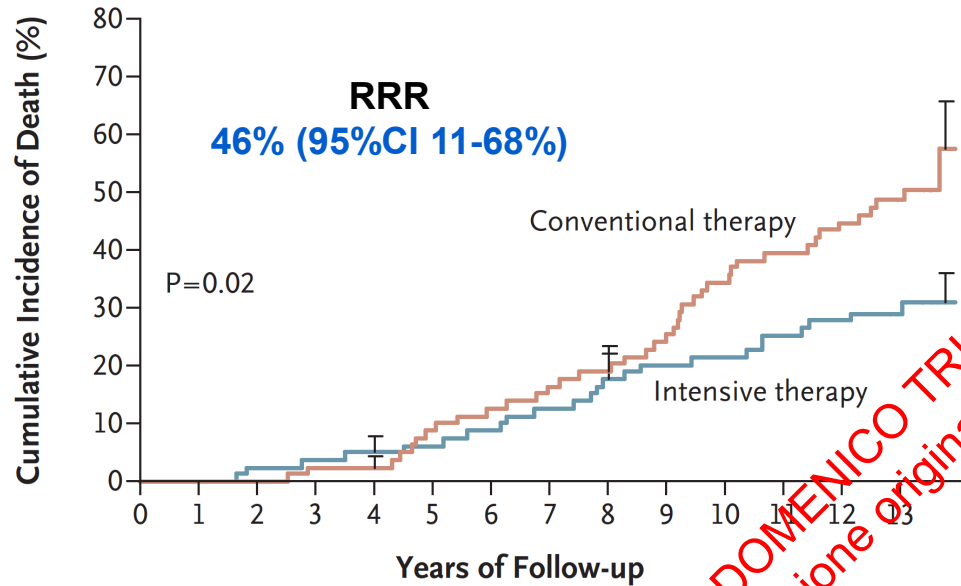
| Variable                                                                   | Conventional Therapy |           | Intensive Therapy |           |
|----------------------------------------------------------------------------|----------------------|-----------|-------------------|-----------|
|                                                                            | 1993–1999            | 2000–2001 | 1993–1999         | 2000–2001 |
| Systolic blood pressure (mm Hg)                                            | <160                 | <135      | <140              | <130      |
| Diastolic blood pressure (mm Hg)                                           | <95                  | <85       | <85               | <80       |
| Glycosylated hemoglobin (%)                                                | <7.5                 | <6.5      | <6.5              | <6.5      |
| Fasting serum total cholesterol (mg/dl)                                    | <250                 | <190      | <190              | <175      |
| Fasting serum triglycerides (mg/dl)                                        | <195                 | <180      | <150              | <150      |
| Treatment with ACE inhibitor irrespective of blood pressure                | No                   | Yes       | Yes               | Yes       |
| Aspirin therapy                                                            |                      |           |                   |           |
| For patients with known ischemia                                           | Yes                  | Yes       | Yes               | Yes       |
| For patients with peripheral vascular disease                              | No                   | No        | Yes               | Yes       |
| For patients without coronary heart disease or peripheral vascular disease | No                   | No        | No                | Yes       |

**Intensive therapy:** Stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of CV disease with aspirin.

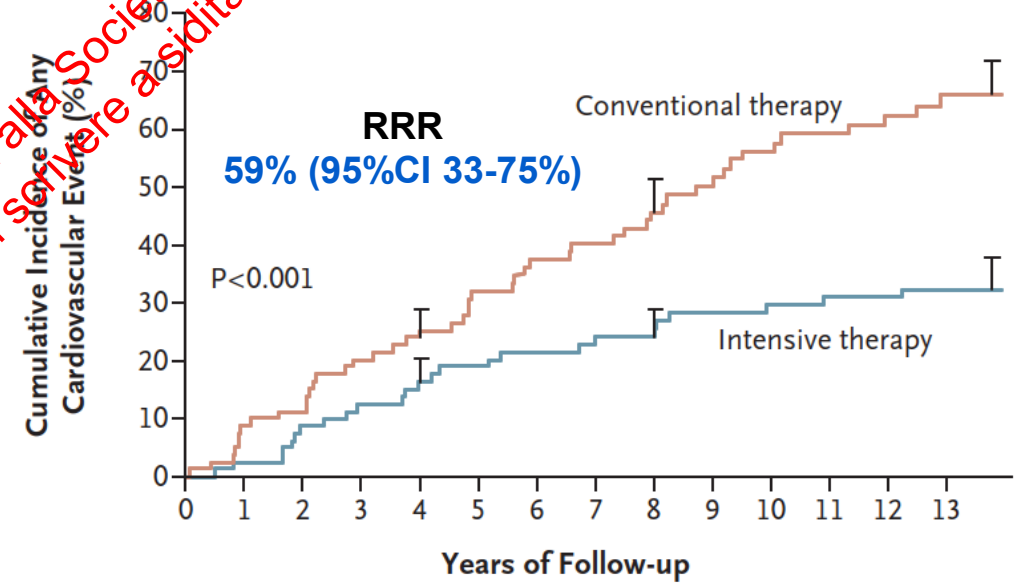
# Legacy effect of intensive multiple risk factor control: Steno-2



# Legacy effect of intensive multiple risk factor control: Steno-2

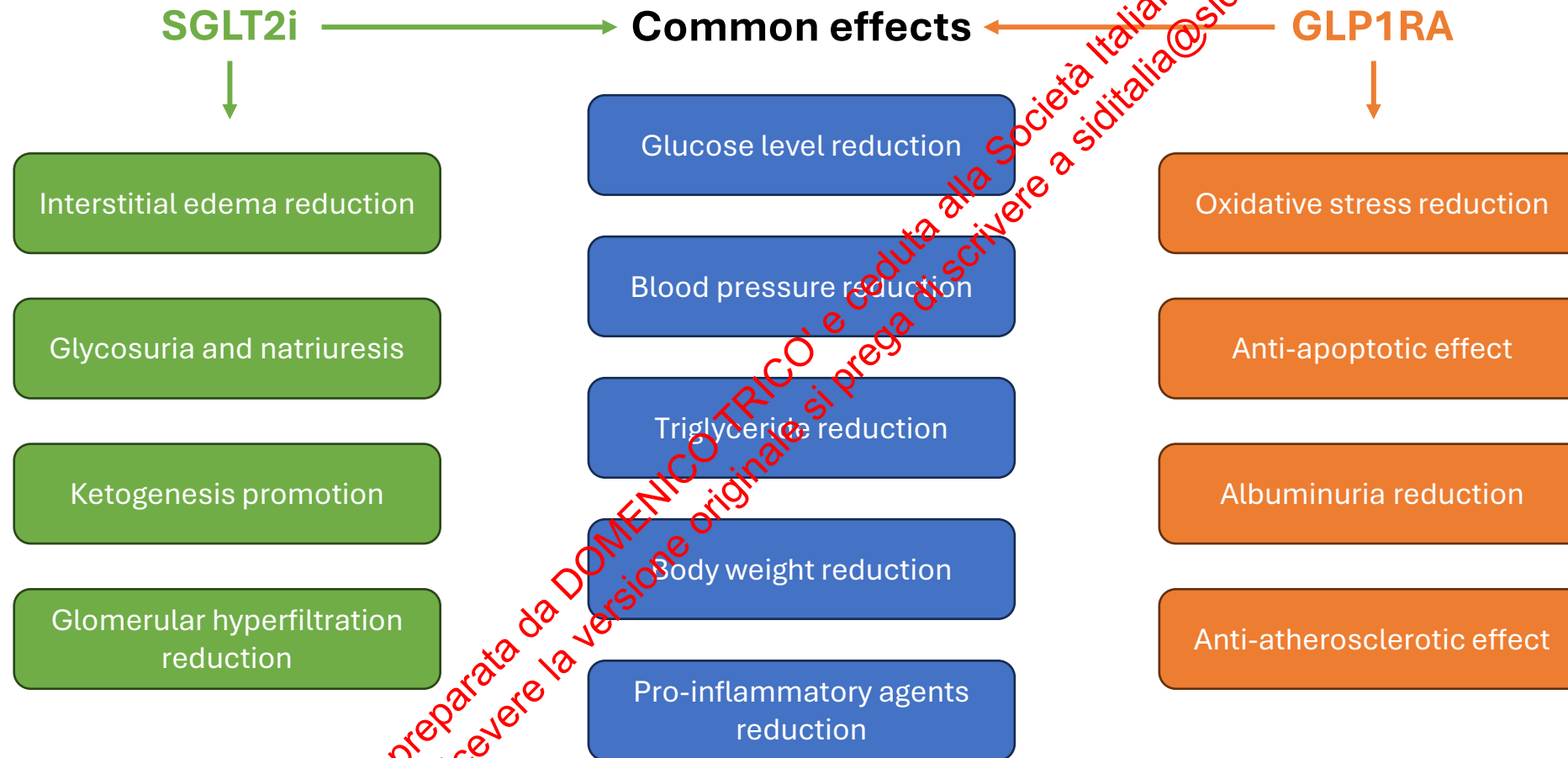


| No. at Risk          |    |    |    |    |    |    |    |    |  |
|----------------------|----|----|----|----|----|----|----|----|--|
| Intensive therapy    | 80 | 78 | 75 | 72 | 65 | 62 | 57 | 39 |  |
| Conventional therapy | 80 | 80 | 77 | 69 | 63 | 51 | 43 | 30 |  |



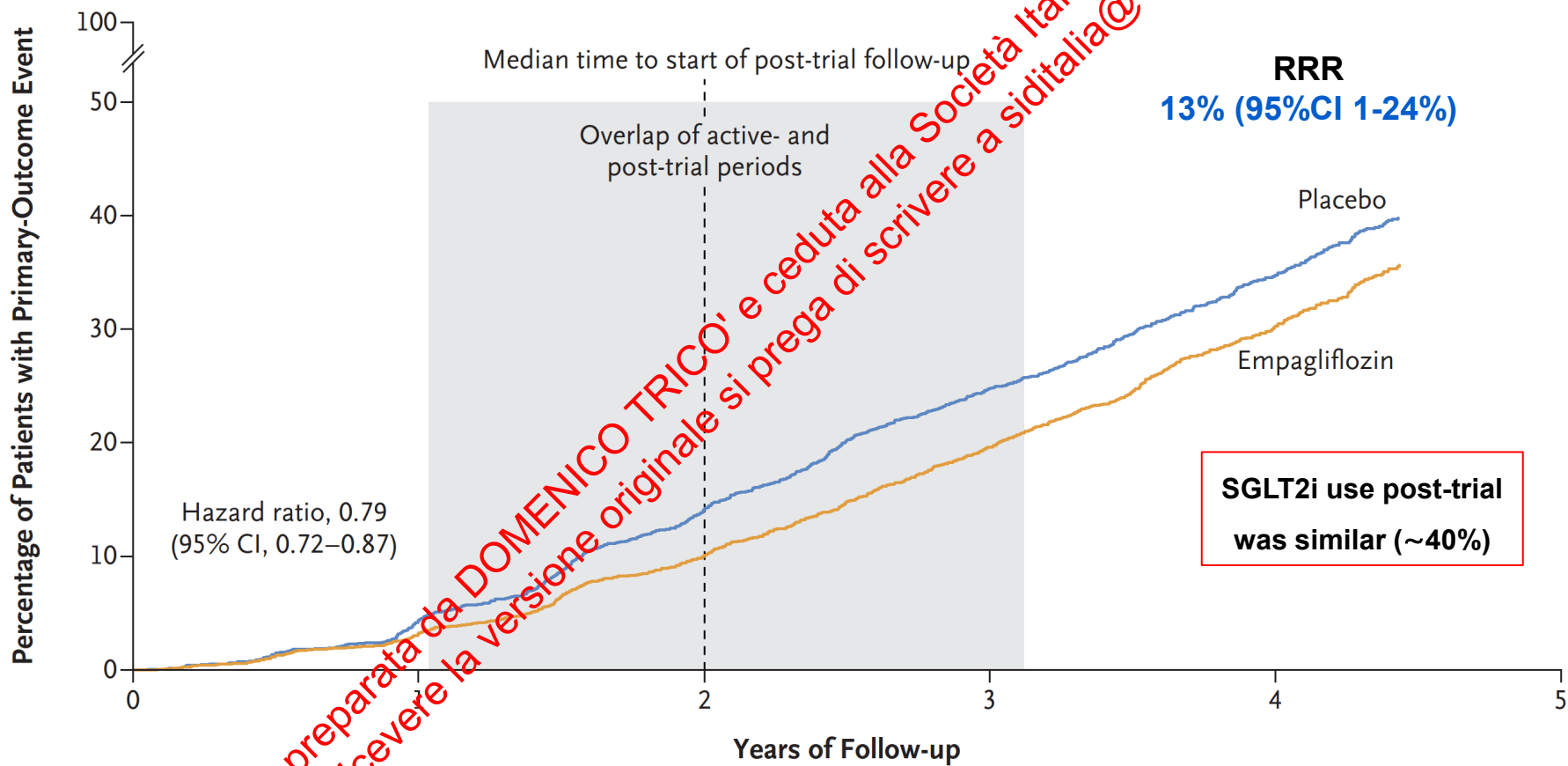
| No. at Risk          |    |    |    |    |    |    |    |    |  |
|----------------------|----|----|----|----|----|----|----|----|--|
| Intensive therapy    | 80 | 72 | 65 | 61 | 56 | 50 | 47 | 31 |  |
| Conventional therapy | 80 | 70 | 60 | 46 | 38 | 29 | 25 | 14 |  |

# Beneficial actions of SGLT2i and GLP1RA



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# Legacy effect of early SGLT2i use



**Primary Outcome:** Kidney disease progression or CV death.

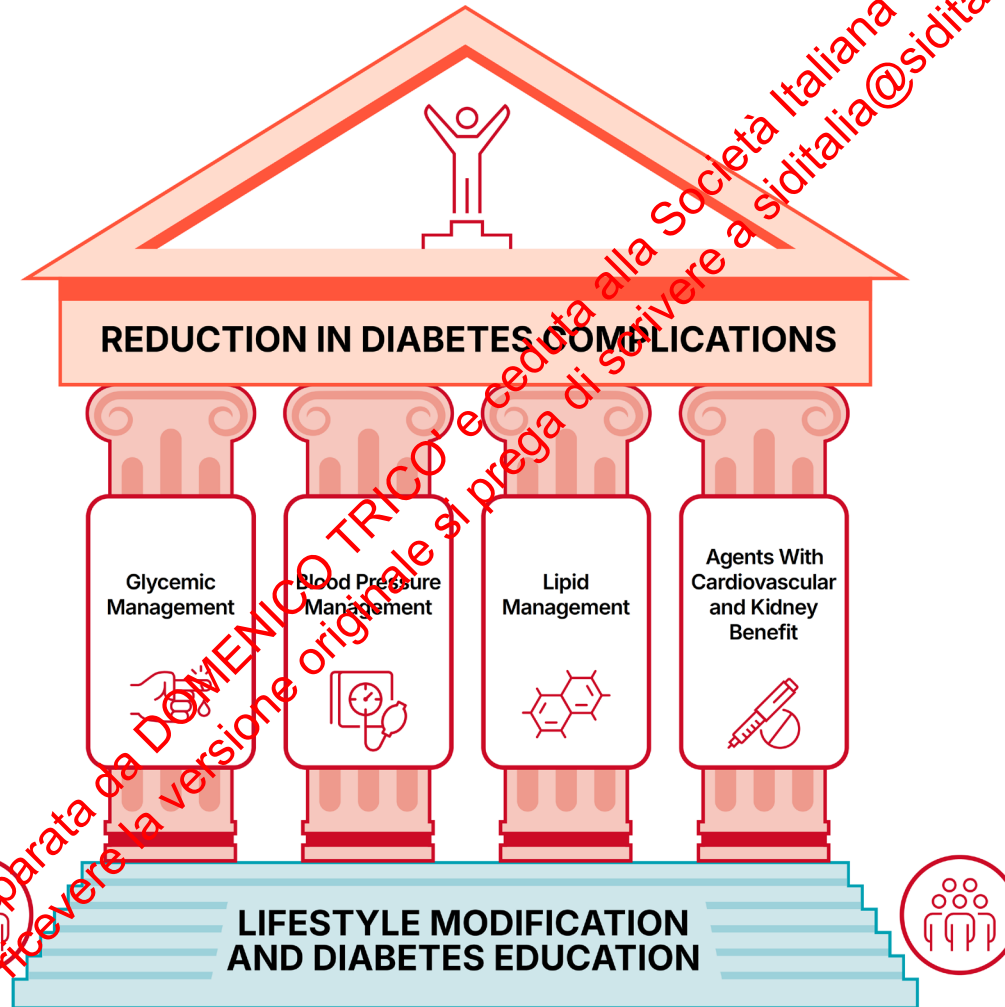
EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2025

# Legacy effect of early GLP-1 RA use

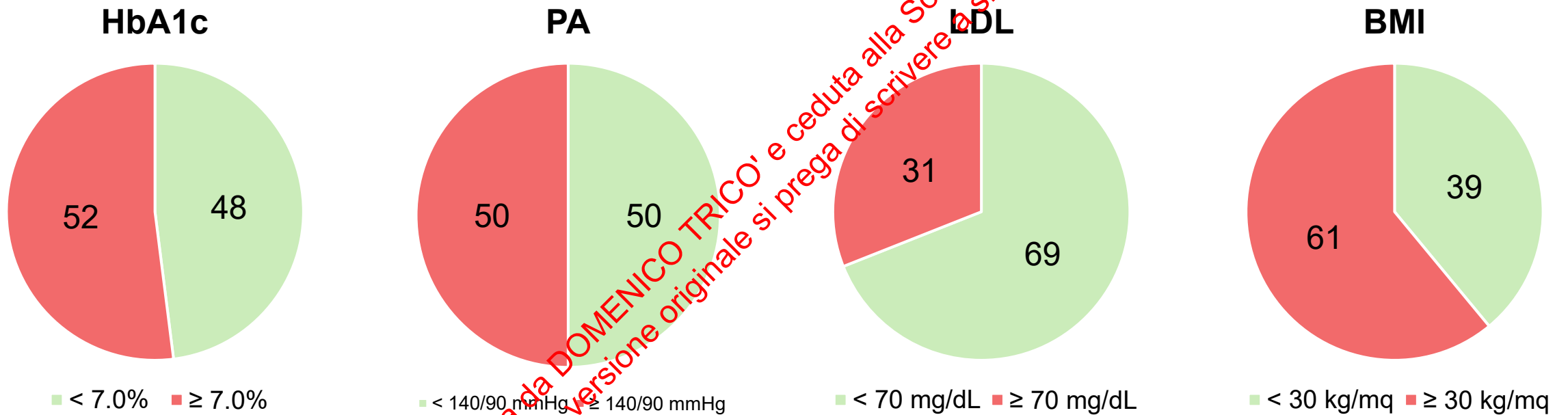
## Multivariable time dependent Cox regression analysis for MACE

|                                 | HR (95% CI)      | p       |
|---------------------------------|------------------|---------|
| <i>Primary prevention</i>       |                  |         |
| Age at beginning of GLP1, years | 1.08 (1.03–1.14) | 0.001   |
| GLP-1 RA withdrawal by time     | 3.40 (1.82–6.32) | < 0.001 |
| <i>Secondary prevention</i>     |                  |         |
| GLP-1 RA withdrawal by time     | 2.71 (1.46–5.01) | 0.002   |

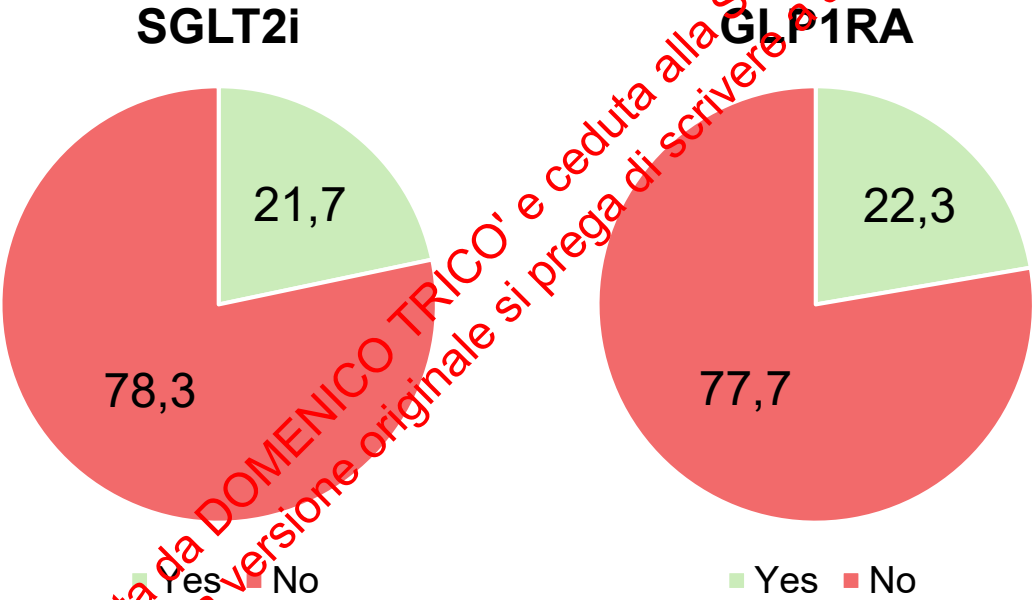
# Pillars of cardiovascular risk management in diabetes



# CV risk factor control in people T2D in Italy



# Use of agents with cardiorenal benefits in people T2D in Italy



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# Summary

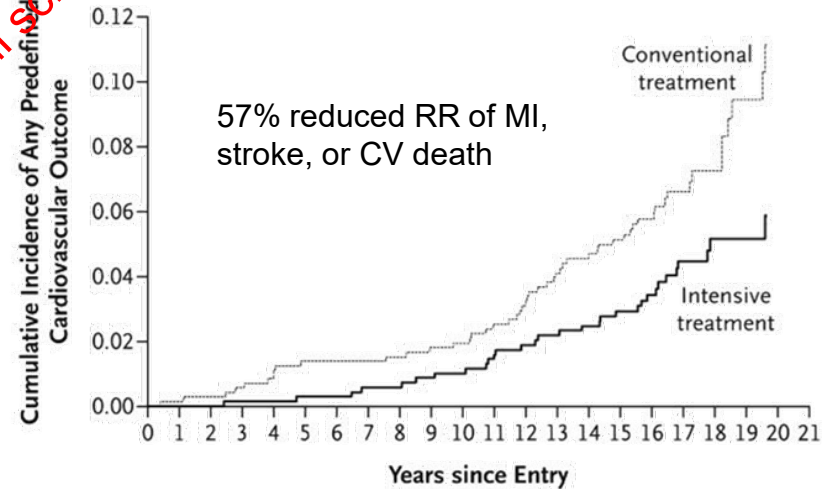
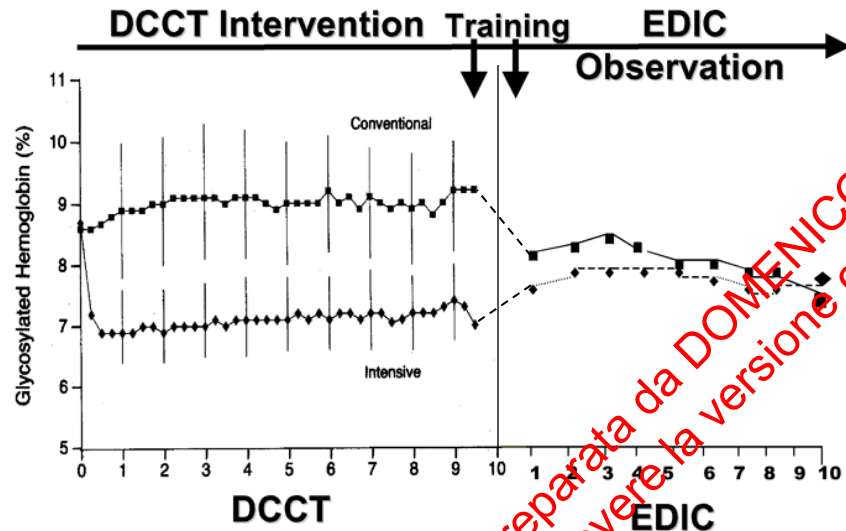
- Type 2 diabetes is a progressive, multifactorial disease requiring comprehensive management.
- Early preventive interventions and tight risk factor control are associated with longer-term benefits.
- Initiating pharmacological agents with proven cardiovascular benefits early improves clinical outcomes.
- Despite robust evidence, therapeutic inertia remains a major barrier to optimal diabetes care.

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# Legacy effect: Definition

A phenomenon of continuous beneficial effect of the intensive control on disease outcomes or complications even after a long duration of cessation of the intervention.



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| Intensive treatment    | 705 | 683 | 629 | 113 |
| Conventional treatment | 714 | 688 | 618 | 92  |

# Legacy effect of intensive glycemic control

| Study<br>(median HbA1c intensive<br>vs conventional) | Microvascular complications                                                         |                                                                                     | Macrovascular complications                                                           |                                                                                       | Cardiovascular mortality                                                               |                                                                                        |
|------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| <b>UKPDS</b><br>7.0% vs 7.9%                         |    |  |    |    |  ** |  ** |
| <b>ACCORD</b><br>6.4% vs 7.5%                        | N/R                                                                                 | N/R                                                                                 |    |    |     |     |
| <b>ADVANCE</b><br>6.4% vs 7.0%                       |    |  |    |    |     |     |
| <b>VADT</b><br>6.9% vs 8.4%                          |  | N/R                                                                                 |  |  |   |   |

 Initial trial

 Long-term follow up

\* Significant benefit on ESKD only ( $p=0.007$ )

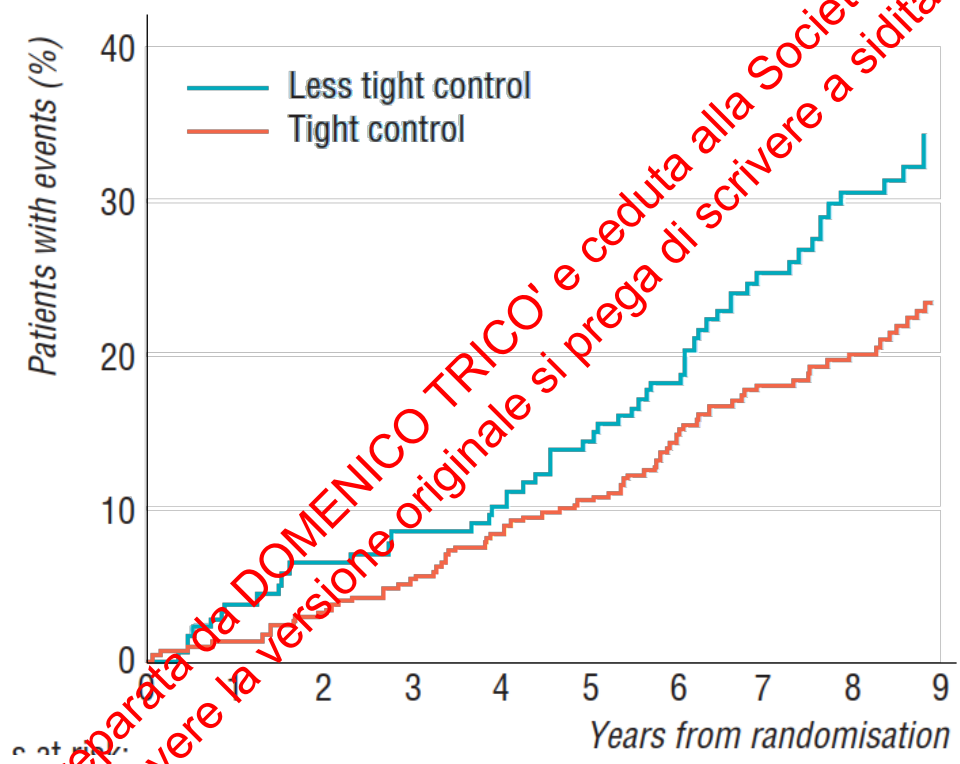
\*\* Diabetes-related mortality

Holman RR et al. N Engl J Med 2008; ACCORD group. Diabetes Care 2016;

Zoungas S et al. N Engl J Med 2014; Hayward RA et al. N Engl J Med 2015

# Legacy effect of intensive blood pressure control: UKPDS

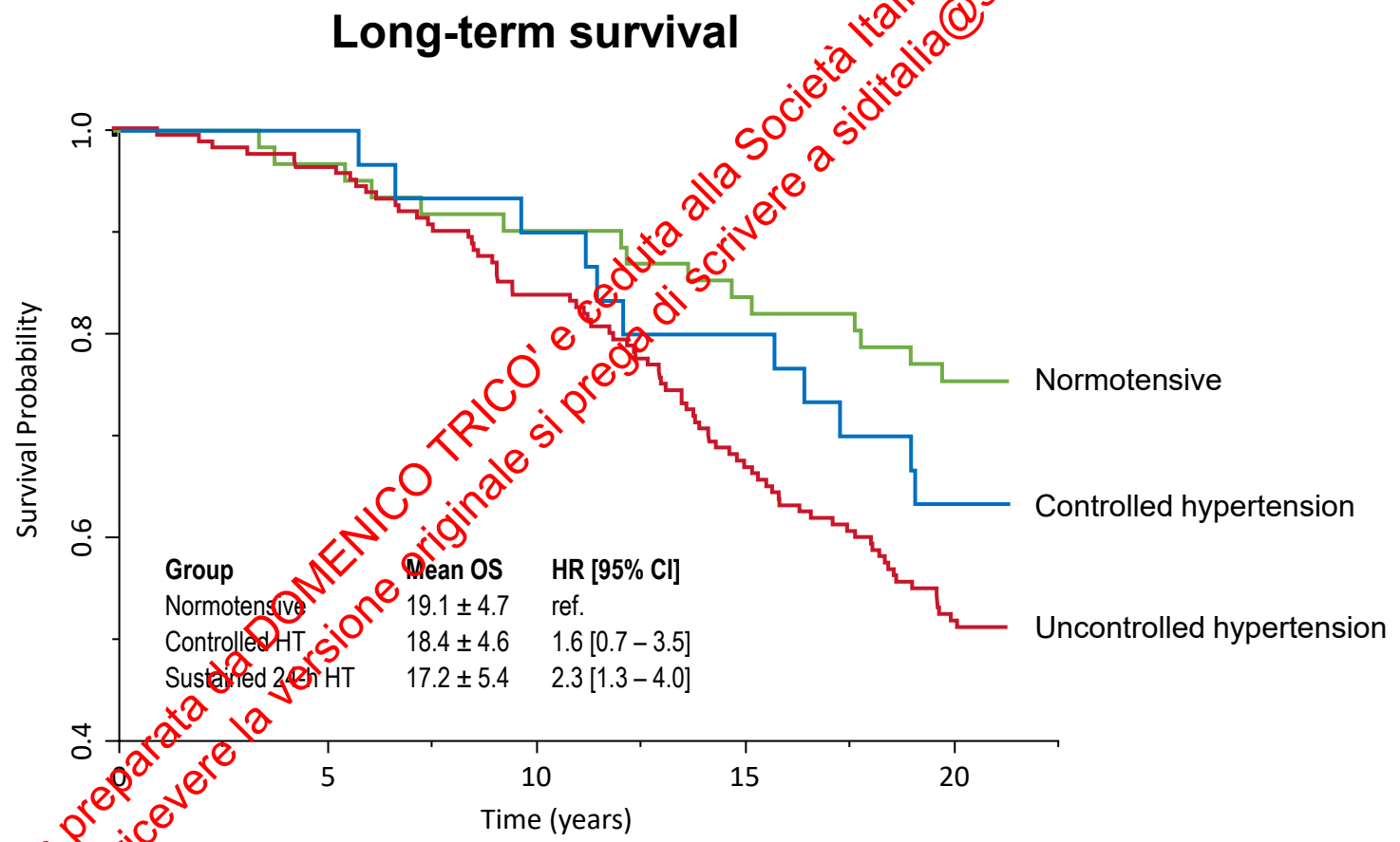
Death for diabetes-related disease \*



RR reduction  
32% (95%CI 6-51%)

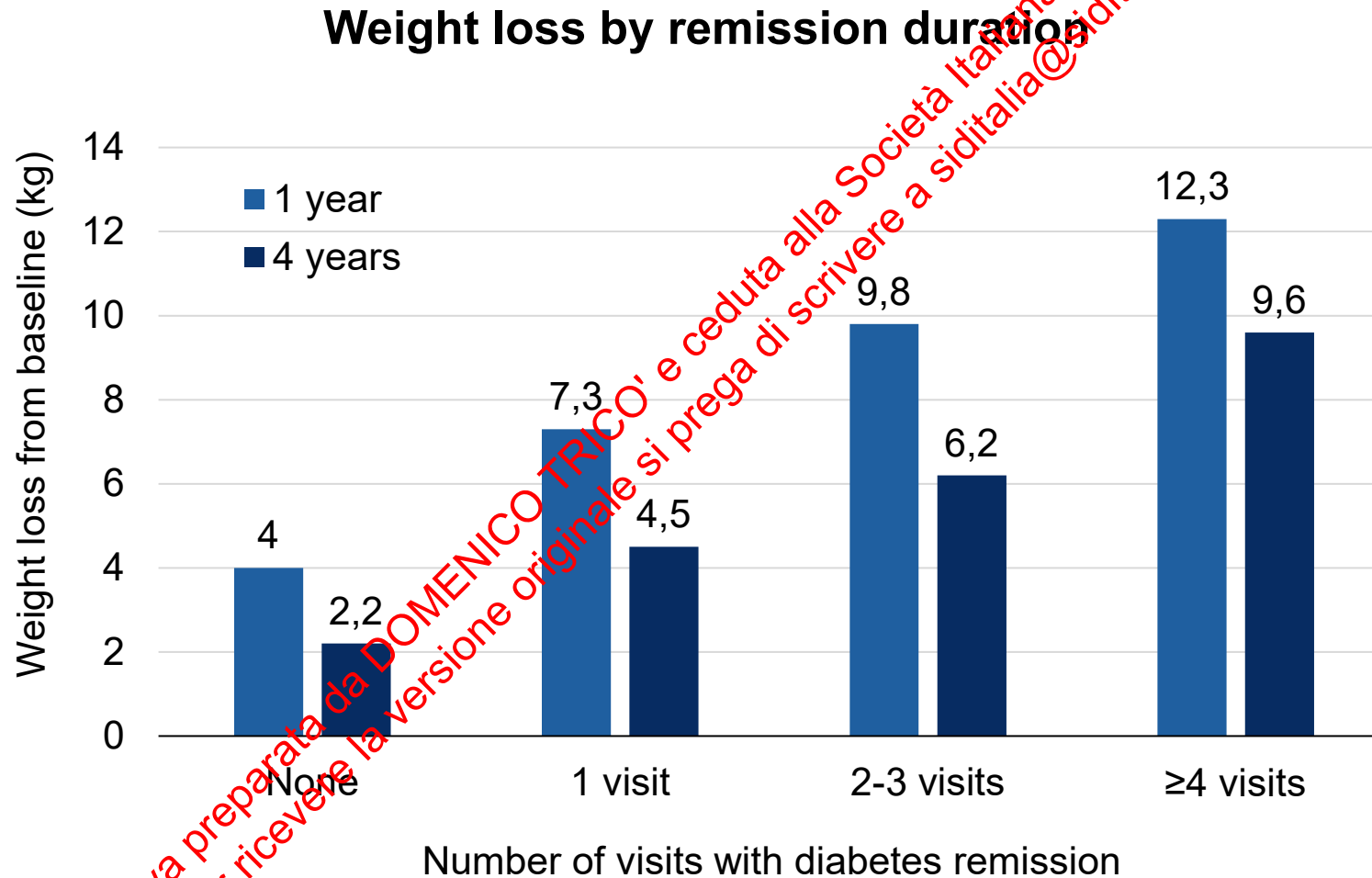
\* Myocardial infarction, sudden death, stroke, peripheral vascular disease, and renal failure.  
'Tight' control: average 144/82 mmHg vs 154/87 mmHg

# Legacy effect of intensive blood pressure control: CHAMP10N



\* Adjusted for: age, sex, BMI, glycemic control, eGFR, office SBP, type and duration of diabetes.  
Current diagnostic criteria and therapeutic target using 24-h ABPM

# Legacy effect of intensive body weight control: Look-AHEAD



**Intensive intervention:** Low-calorie diet (1200-1800 kcal/die) with 1-2 meal replacements and >175 min/week moderate physical activity. Weekly visits for 6 months, then fortnightly visits up to 4 years.