La lezione dei trials di safety cardiovascolare

Edoardo Mannucci
Conflitti di interessi

Negli ultimi due anni, E. Mannucci ha ricevuto compensi per relazioni e/o consulenze da:

*Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, and Takeda.*

La struttura diretta da E. Mannucci ha ricevuto donazioni, finanziamenti per ricerca o compensi per trial clinici da:

*AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, and Novo Nordisk.*
FDA Guidance for CV safety of new drugs for diabetes

- Perform meta-analyses of Phase II/III trials (or specific Phase III cardiovascular [CV] outcome studies), to assess the risk of major CV events

<1.3 – a post-marketing cardiovascular trial may not generally be necessary

<1.8 – conduct large safety trial post-approval

>1.8 – conduct large safety trial pre-approval

CV safety studies for diabetes drugs

Methodological issues

- Designed for non-inferiority (event-driven, target 611 events)
- Enrollment of very high-risk patients
- Relatively short duration of follow-up
- Attempt at minimizing between-group differences in glucose control
Saxagliptin: effect on major cardiovascular events

Results of the SAVOR-TIMI trial

Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

16,492 T2DM patients with prior CVD/high CV risk, saxagliptin vs placebo 1:1.
Follow-up: 2.1 y

Alogliptin: effect on major cardiovascular events

Results of the EXAMINE trial

**Principal endpoint:**
3-point MACE (nonfatal MI, nonfatal stroke, and cardiovascular death)

5380 T2DM patients with recent acute coronary syndrome, alogliptin vs placebo 1:1.
Follow-up: 1.5 y

Sitagliptin: effect on major cardiovascular events

Results of the TECOS trial

**Principal endpoint:**
4-point MACE (nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

14,671 T2DM patients with prior CVD, sitagliptin vs placebo 1:1. Follow-up: 3 y

Lixisenatide: effect on major cardiovascular events

Results of the ELIXA trial

Principal endpoint:
4-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

6068 T2DM patients with recent acute coronary syndrome, lixisenatide vs placebo 1:1. Follow-up: 2.1 y

Liraglutide: effect on major cardiovascular events

Results of the LEADER trial

Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

9,340 T2DM patients with prior cardiovascular disease and/or high CV risk, Liraglutide vs placebo 1:1.
Follow-up: 4 y

Liraglutide: effect on all-cause mortality

Results of the LEADER trial

Secondary endpoint:
All-cause mortality

9,340 T2DM patients with prior cardiovascular disease and/or high CV risk, Liraglutide vs placebo 1:1. Follow-up: 4 y

Exenatide LAR: effect on major cardiovascular events

Results of the EXSCEL trial

Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

14,752 T2DM patients with prior cardiovascular disease and/or high CV risk, exenatide LAR vs placebo 1:1. Follow-up: 3.2 y

Exenatide LAR: effect on all-cause mortality

Results of the EXSCEL trial

**Principal endpoint:**
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

14,752 T2DM patients with prior cardiovascular disease and/or high CV risk, exenatide LAR vs placebo 1:1. Follow-up: 3.2 y

Empagliflozin: effect on major cardiovascular events

Results of the EMPAREG-OUTCOME trial

**Principal endpoint:**
3-point MACE (nonfatal MI, nonfatal stroke, and cardiovascular death)

9,340 T2DM patients with prior CVD, Empagliflozin vs placebo
Follow-up: 3 y

**NNT:** 62
Canagliflozin: effect on major cardiovascular events

Results of the CANVAS and CANVAS-R trial

**Principal endpoint:**
3-point MACE (nonfatal MI, nonfatal stroke, and cardiovascular death)

10,142 T2DM patients with prior CVD or multiple risk factors,
Canagliflozin vs placebo
Follow-up: 3.6 y

Dapagliflozin vs Glipizide: long-term effects on blood pressure

Results of a RCT, add-on to metformin

Principal endpoint:
HbA1c

Extension of a RCT on 814 patients with T2DM inadequately controlled on metformin

Empagliflozin: effect on cardiovascular mortality

Predicted and observed results of the EMPAREG-OUTCOME trial

Actually observed figures: MACE -14%, CV mortality -38%

Luconi M, Raimondi L, Di Franco A, Mannucci E

*Nutr Metab Cardiovasc Dis* 26:1071-8, 2016
Liraglutide vs orlistat: effect on body weight

RCT, obese non-diabetic patients

Dulaglutide vs glargine: effect on HbA1c

Principal endpoint:
A1c at 52 wk

RCT, add-on to metformin and SU; AWARD-2

810 T2DM patients inadequately controlled with metformin plus SU, Dulaglutide vs glargine. Follow-up: 78 wk

Semaglutide vs dulaglutide: effect on HbA1c and FPG

Results of the SUSTAIN-7 trial

**Principal endpoint:**
HbA1c at 40 wk

1,201 T2DM patients with HbA1c>7, Add-on to metformin

Semaglutide: effect on major cardiovascular events

Results of the SUSTAIN-6 trial

Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

3,297 T2DM patients with prior cardiovascular disease and/or high CV risk, Semaglutide vs placebo 1:1. Follow-up: 2 y

Glycemic control and risk of MI in T2DM

Meta-analysis of RCTs on intensification of therapy

Glycemic control and cardiovascular risk in type 2 DM

Summary of CVOTs and RCTs on intensification of therapy

Mannucci E, Monami M, Ceriello A, Rotella CM. *Nutr Metab Cardiovasc Dis*, 2017
GLP1 receptor agonists: cardiovascular actions

Empagliflozin: effect on heart failure

Results of the EMPAREG-OUTCOME trial

Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

9,340 T2DM patients with prior CVD, Empagliflozin vs placebo
Follow-up: 3 y

Canagliflozin: effect on heart failure

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Follow-up: 3.6 y

Empagliflozin: effect on all-cause mortality

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Secondary endpoint:
All-cause mortality

9,340 T2DM patients with prior CVD, Empagliflozin vs placebo
Follow-up: 3 y

Empagliflozin: effect on cardiovascular mortality

Predicted and observed results of the EMPAREG-OUTCOME trial

Actually observed figures: MACE -14%, CV mortality -38%

Luconi M, Raimondi L, Di Franco A, Mannucci E

*Nutr Metab Cardiovasc Dis* 26:1071-8, 2016
**Standard italiani per la cura del diabete mellito**  
*Edizione 2018*

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**Tabella 4.H2. Benefici dei farmaci per il diabete di tipo 2.**

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Drugs for T2DM and CV risk

Open issues

• The actual impact of drugs for T2DM on CV risk could be underestimated: efficacy CVOT trials are needed

• The contribution of traditional risk factors and unconventional mechanisms of CV protection with different classes of drugs needs to be further clarified

• Available data are focused on secondary prevention/very high risk patients; data on primary prevention/lower risk patients are needed