

Dapagliflozin and Outcomes in Patients with Peripheral Artery Disease: Insights from DECLARE-TIMI 58

Marc P. Bonaca MD MPH
for the DECLARE – TIMI 58 Investigators
American College of Cardiology
March 2019

Diabetes and peripheral artery disease (PAD) are frequently comorbid conditions

SGLT2 inhibitors:

- **Reduce heart failure and renal complications in patients with diabetes**
- **Have been associated with amputation risk with 1 available agent but not the other 2; however, trials thus far have not been designed to evaluate amputation or limb ischemic events**
- **To date, a detailed examination of all limb ischemic events in high-risk subpopulations has not been performed**

Trial Design

17,160 with Type 2 DM and
Established CV Disease (6974 incl **1025 w/PAD**) or MRF (10186)
PAD Inclusion Criteria:
**Current claudication + ABI < 0.90 or history of peripheral
revascularization or amputation for ischemia**

DAPAGLIFLOZIN
10 mg DAILY

RANDOMIZE 1:1
DOUBLE BLIND
All other DM Rx per treating MD

PLACEBO

Follow-up visits
In Person Q 6 mo/ telephone Q 3 mo

Primary EPs
Safety: MACE (CVD/MI/Ischemic Stroke)
Dual Efficacy: CVD/HHF, MACE

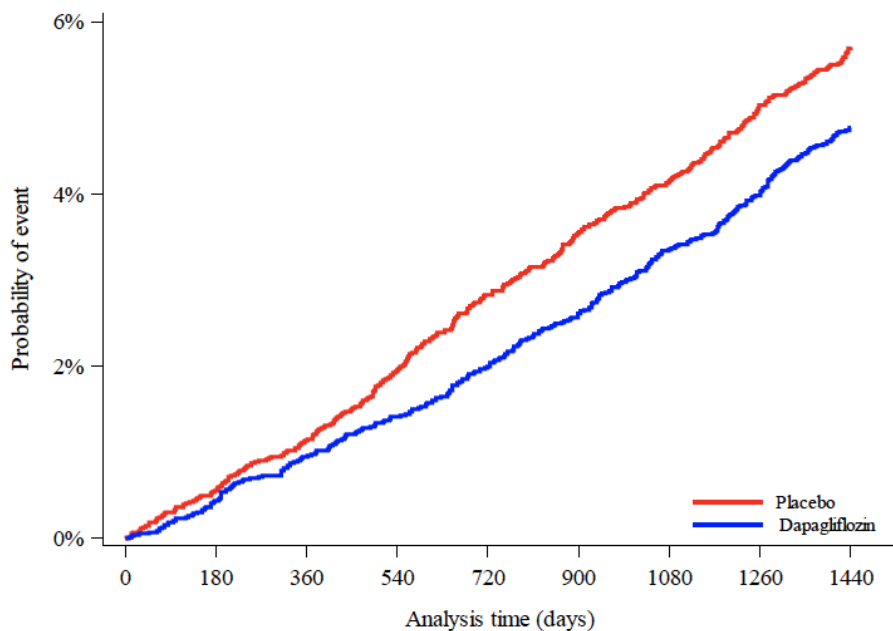
Median follow up
4.2 years

CVD/HHF

4.9% vs 5.8%

HR 0.83 (0.73-0.95)

P(Superiority) 0.005



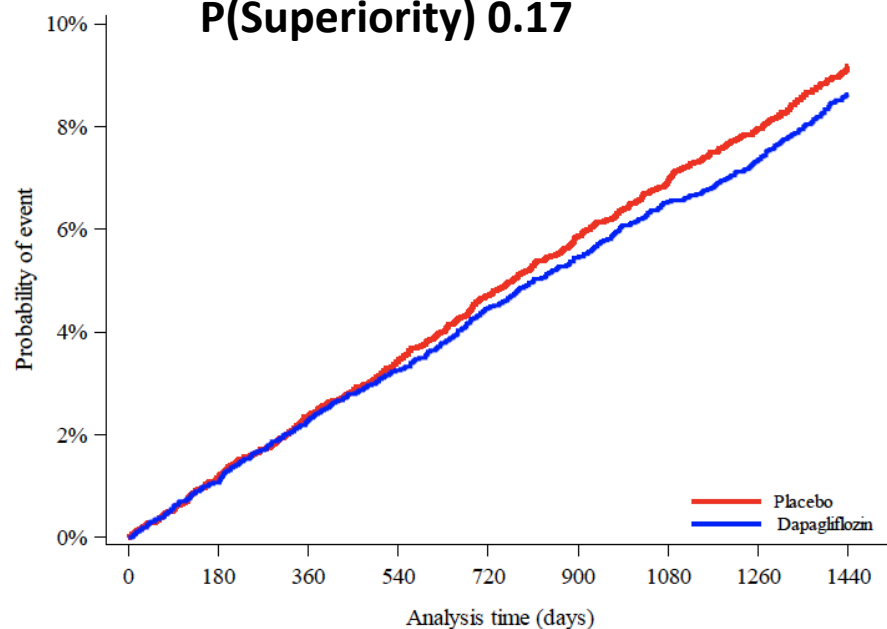
MACE

8.8% vs 9.4%

HR 0.93 (0.84-1.03)

P(Noninferiority) <0.001

P(Superiority) 0.17



Cardiac Events:

- **MACE: composite of CV death, MI or ischemic stroke**
- **HHF: Hospitalization for heart failure**

Renal Events:

- **Renal primary: $\geq 40\%$ decrease in eGFR to < 60 ml/minute/1.73 m² of BSA, new ESRD or death from renal or CV causes**

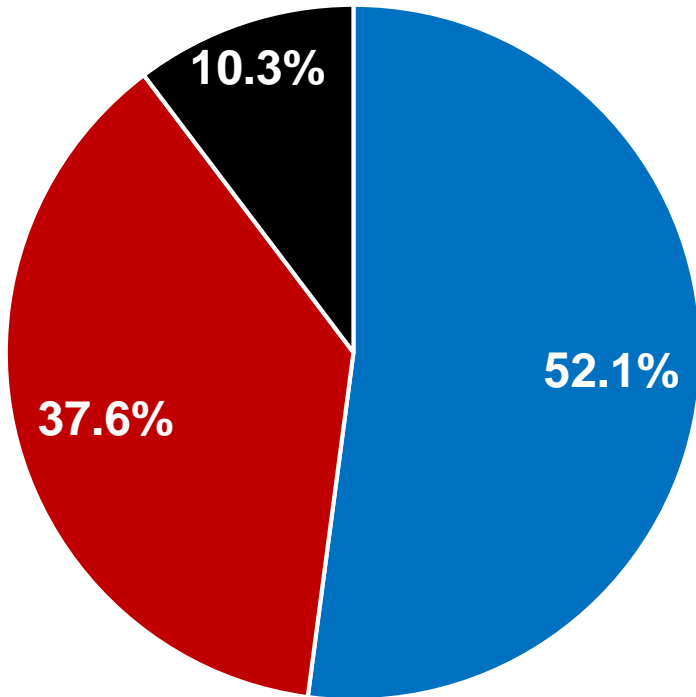
Limb outcomes:

- **Limb ischemic AEs with subset of:**
 - *Acute limb ischemia (ALI)*
 - *Chronic critical limb ischemia (CLI)*
- **Amputations, primary etiology, contributing where multifactorial**
- **Non-coronary revascularizations (urgent and elective)**
- **Major adverse limb events (MALE) – defined as composite of ALI, CLI, amputation for ischemia or urgent revascularization**

1. **To compare the risk of cardiac, renal and limb events in patients with vs. w/o known PAD (in placebo arm)**
2. To evaluate the **efficacy of dapagliflozin vs. placebo for cardiac and renal events in patients with and w/o PAD**
3. **To evaluate the safety of dapagliflozin vs. placebo for limb ischemic events and amputations in:**
 - All patients
 - High risk subgroups including known PAD

| | PAD N=1,025 | No PAD N=16,135 |
|---|-----------------------|---------------------------|
| Age, median (IQR) | 62 (57, 68) | 64 (60, 68) |
| Female sex, % | 32 | 38 |
| Body Mass Index, median (IQR) | 31 (28, 35) | 31 (28, 36) |
| Caucasian, % | 84 | 79 |
| History Hypertension, % | 85 | 90 |
| Current Smoker, % | 23 | 14 |
| Duration of Diabetes (yrs), median (IQR) | 12 (7, 18) | 10 (6, 16) |
| Hemoglobin A1C, % (IQR) | 8 (8, 9) | 8 (7, 9) |
| Insulin, % | 52 | 40 |
| Estimated GFR (CKD-EPI) < 60, % | 11 | 7 |
| History of Ischemic Heart Disease, % | 46 | 32 |
| History of Myocardial Infarction, % | 27 | 20 |
| History of Cerebrovascular Disease, % | 15 | 7 |
| History of CHF, % | 14 | 10 |

PAD Characteristics



- Claudication only
- Prior Revascularization
- Prior Amputation

| Fontaine Classification at Randomization, | % |
|---|----|
| Stage I: Asymptomatic | 25 |
| Stage IIa: Mild claudication | 49 |
| Stage IIb: Moderate-severe claudication | 21 |
| Stage III or IV: Ischemia rest pain, ulceration or gangrene | 6 |

| Ankle Brachial Index Category, | % |
|--------------------------------|----|
| < 0.5 | 5 |
| 0.5-<0.9 | 93 |
| 0.9-<1.4 | 2 |

Hierarchically Defined:

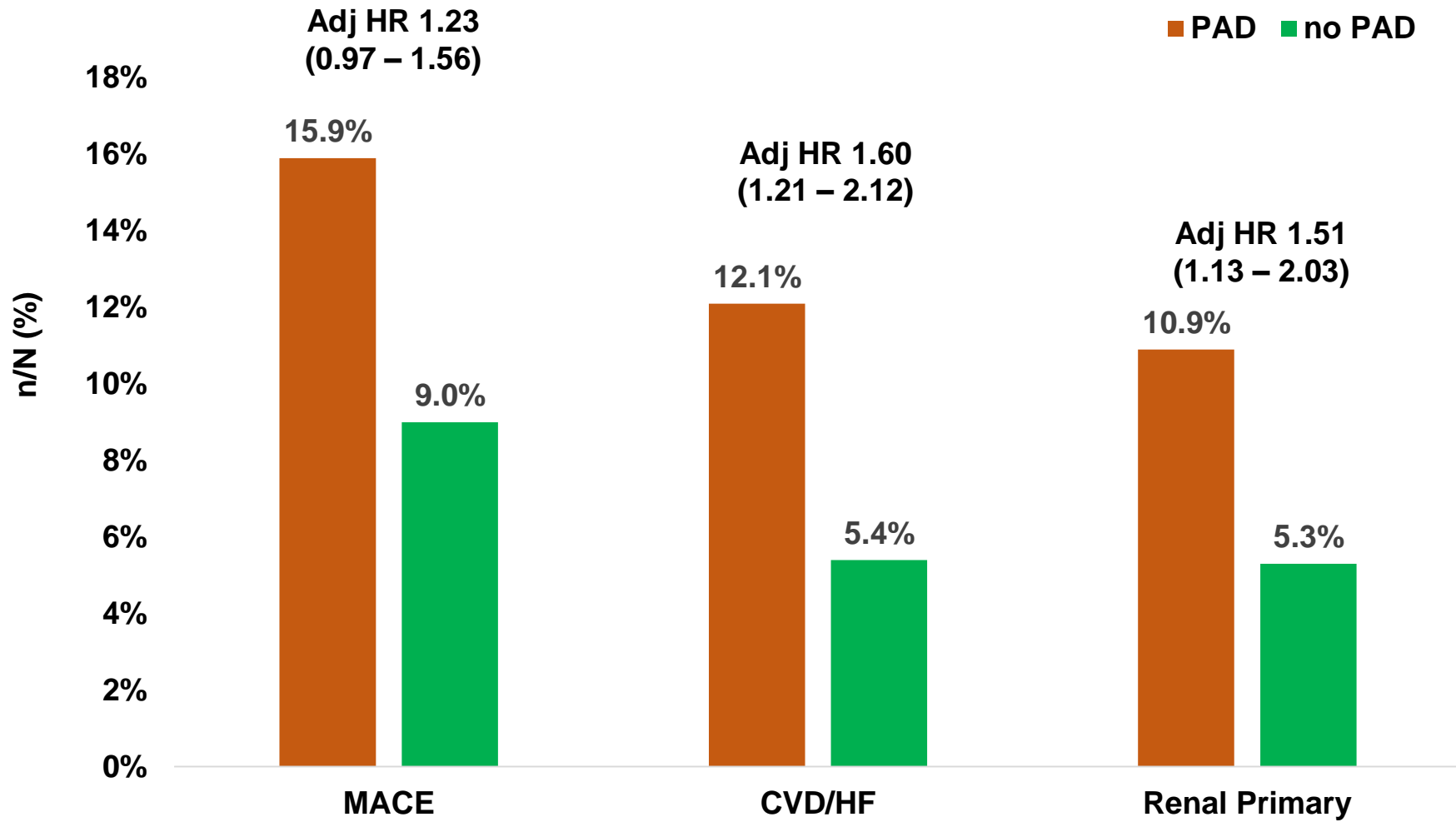
Amputation = any history of amputation regardless of current symptoms

Revascularization = any history of revascularization but no history of amputation

Claudication = claudication with no history of amputation or revascularization

Epidemiology of cardiac, renal and limb outcomes in patients with vs. w/o PAD randomized to placebo

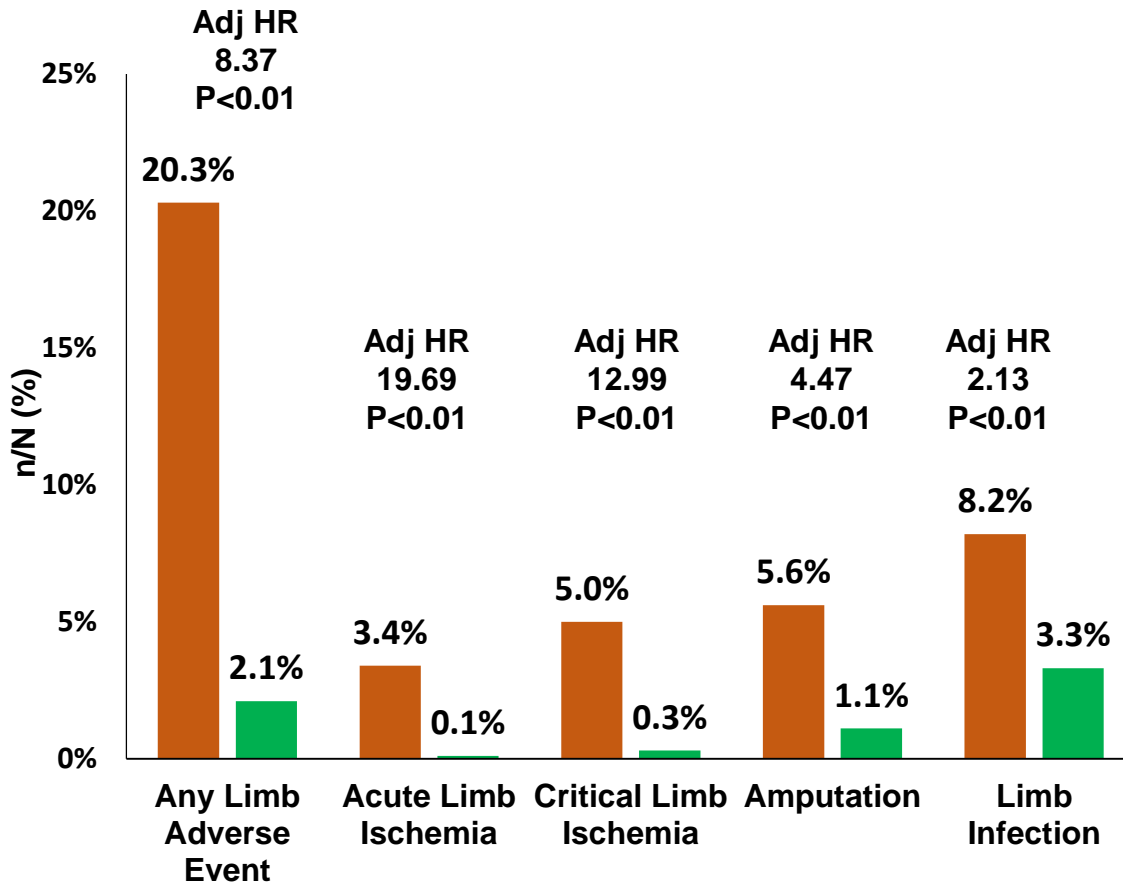
Cardiovascular & Renal Risk by PAD in Placebo Patients



Adjusted for age, sex, race, BMI, hypertension, dyslipidemia, smoking, duration of DM, A1c, eGFR, hx CAD, and hx cerebrovascular disease

Limb Outcomes by PAD Status in Placebo Patients

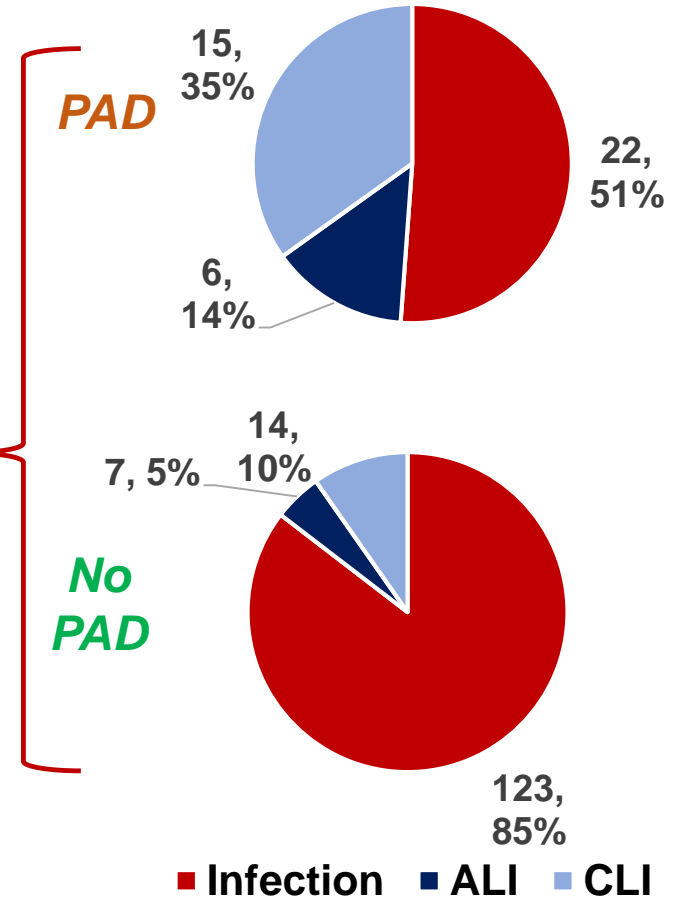
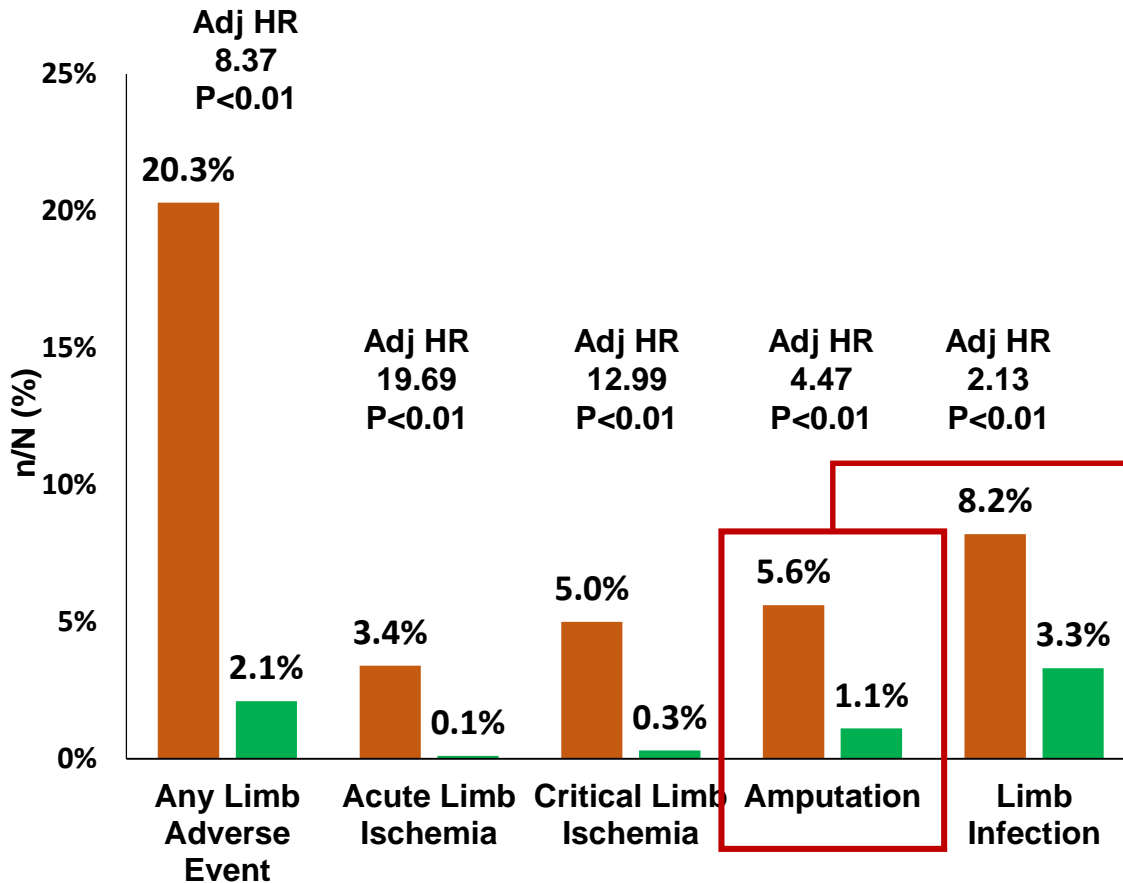
■ PAD ■ no PAD
 N=503 N=8075



Limb Outcomes by PAD Status in Placebo Patients

■ PAD ■ no PAD
 N=503 N=8075

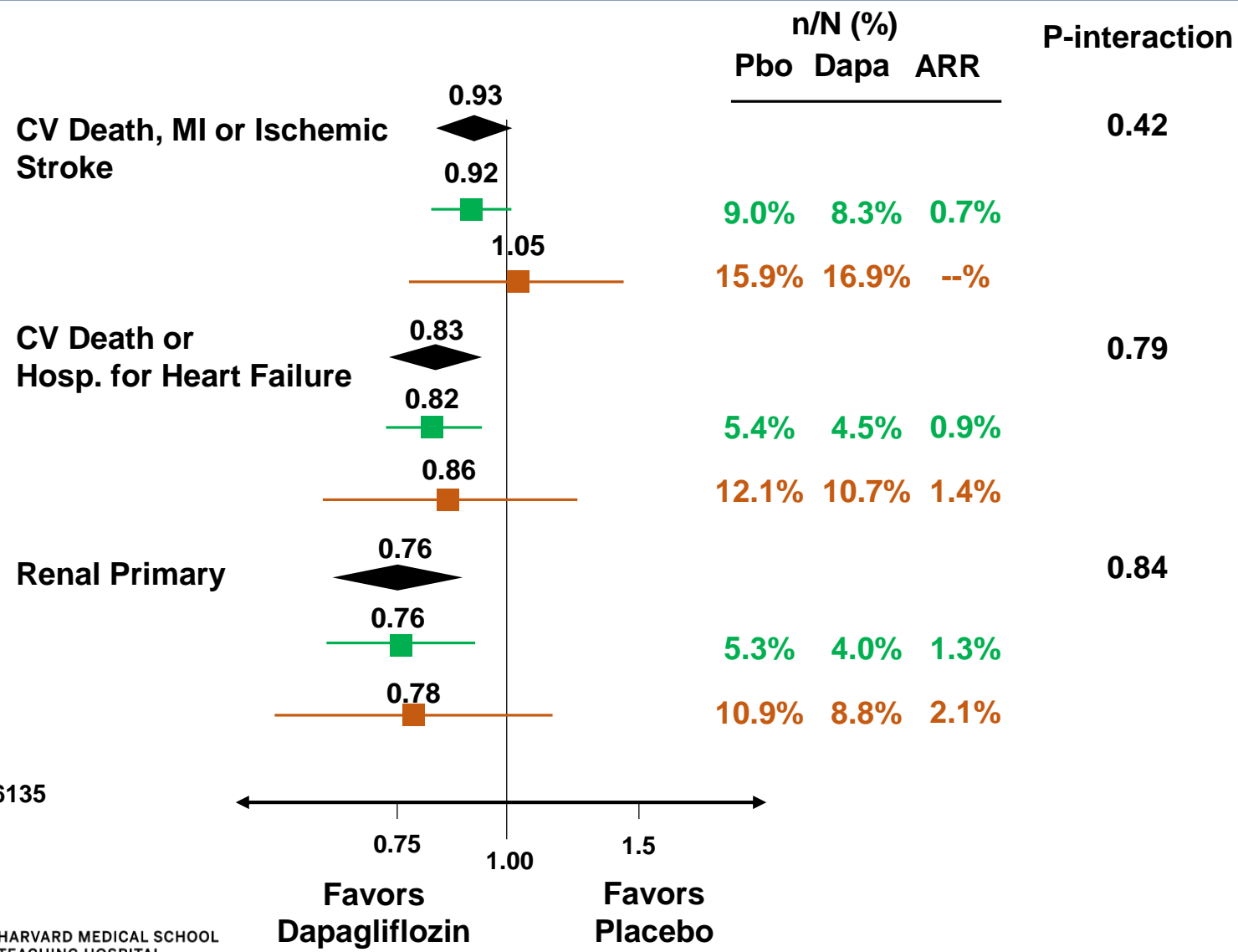
Distribution of Amputation by Primary Etiology*



■ Infection ■ ALI ■ CLI
 *Investigator Reported

Efficacy of Dapagliflozin in Patients with and without PAD

Consistent Benefit of Dapagliflozin in Patients with and without PAD



Safety of Dapagliflozin vs. Placebo for Limb Outcomes in All Patients

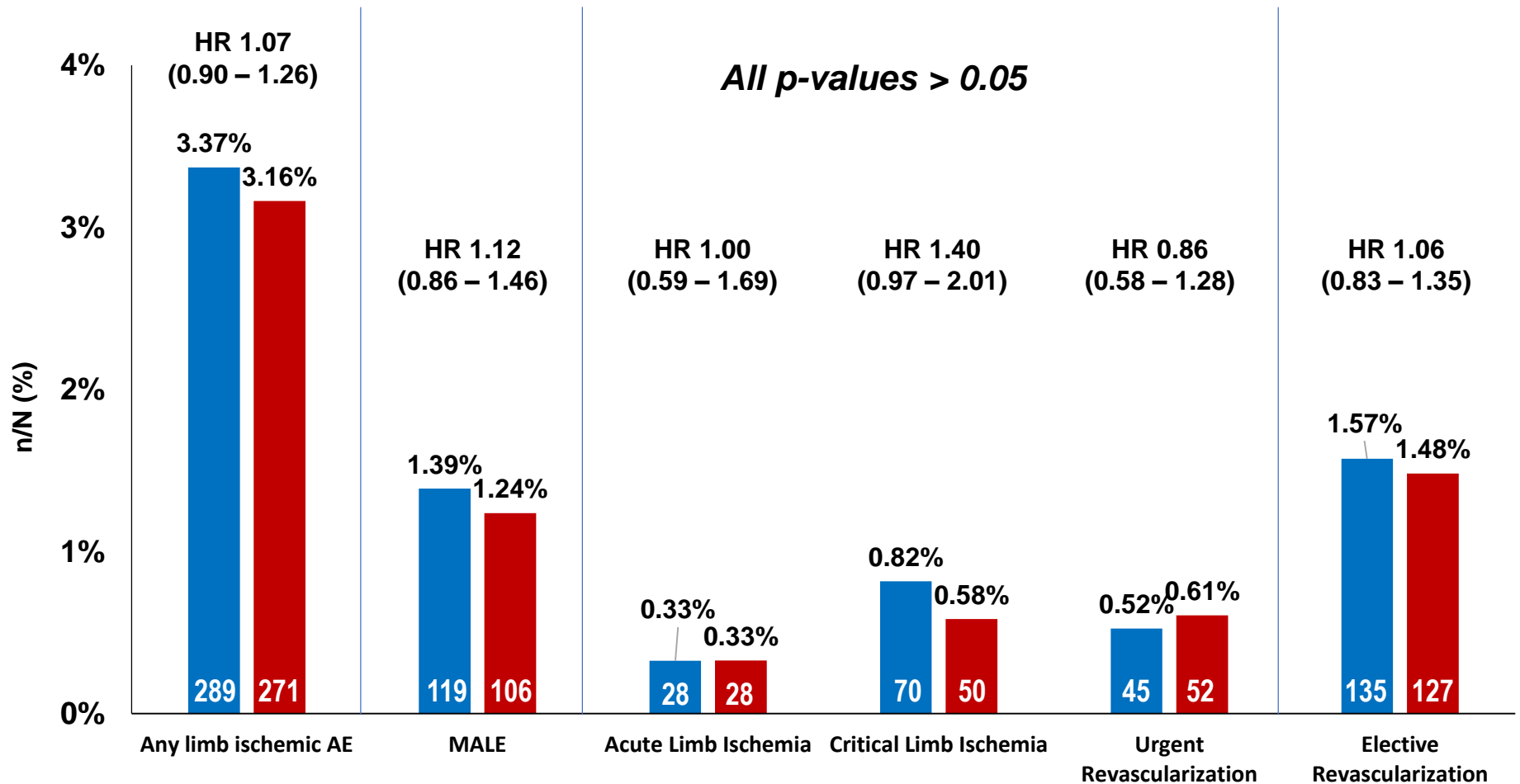


Dapagliflozin and Limb Outcomes

All Patients



DECLARE
TIMI-58
Dapagliflozin Effect on Cardiovascular Events

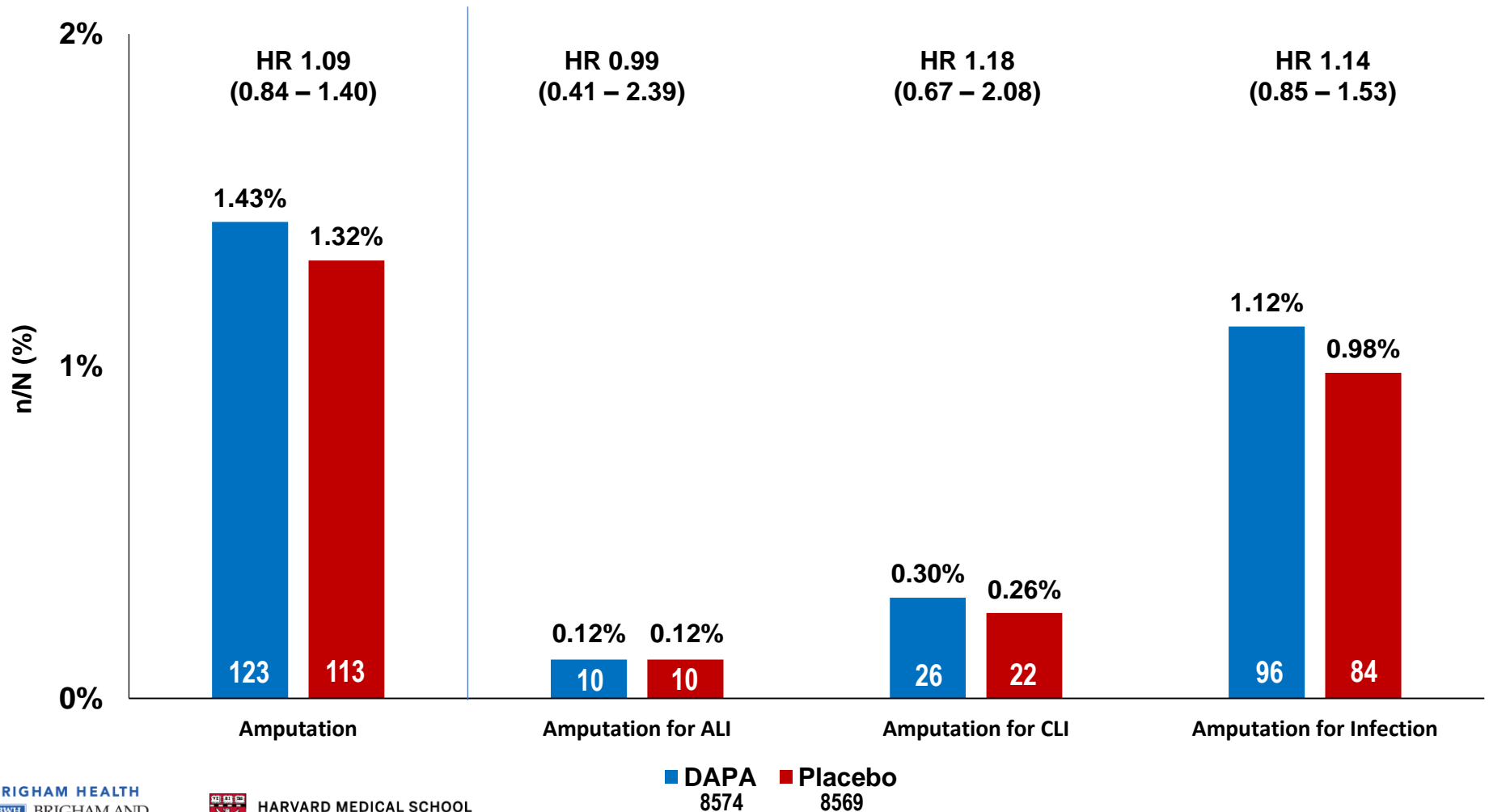


■ DAPA 8574 ■ Placebo 8569

MALE Defined as ALI, CLI, amputation for ischemia or Urgent Revascularization for Ischemia

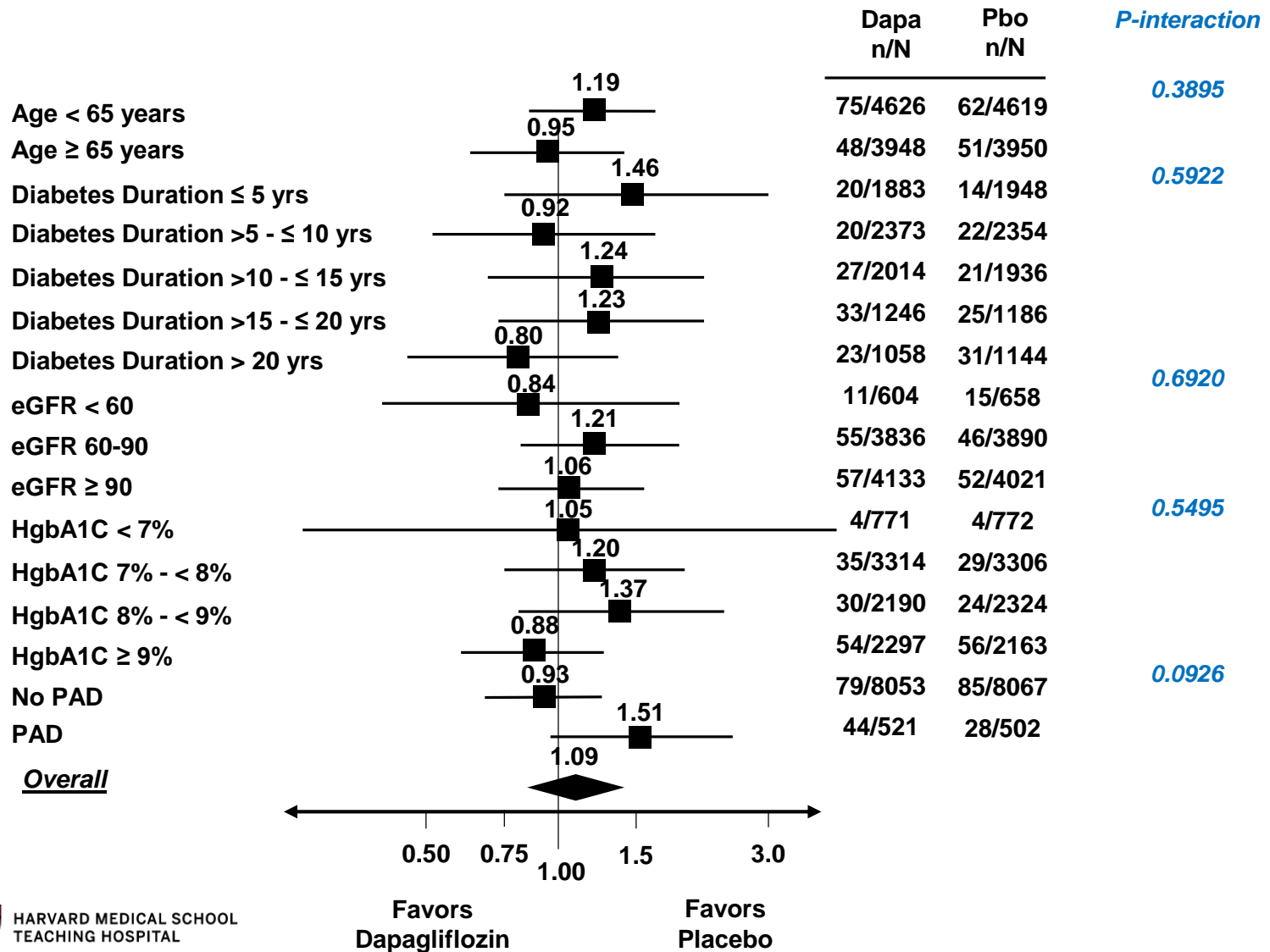
Dapagliflozin and Amputations All Patients

All p-values > 0.05



Safety of Dapagliflozin vs. Placebo for Amputation and Other Limb Events in High Risk Subgroups

Dapagliflozin and Amputation in Key Subgroups





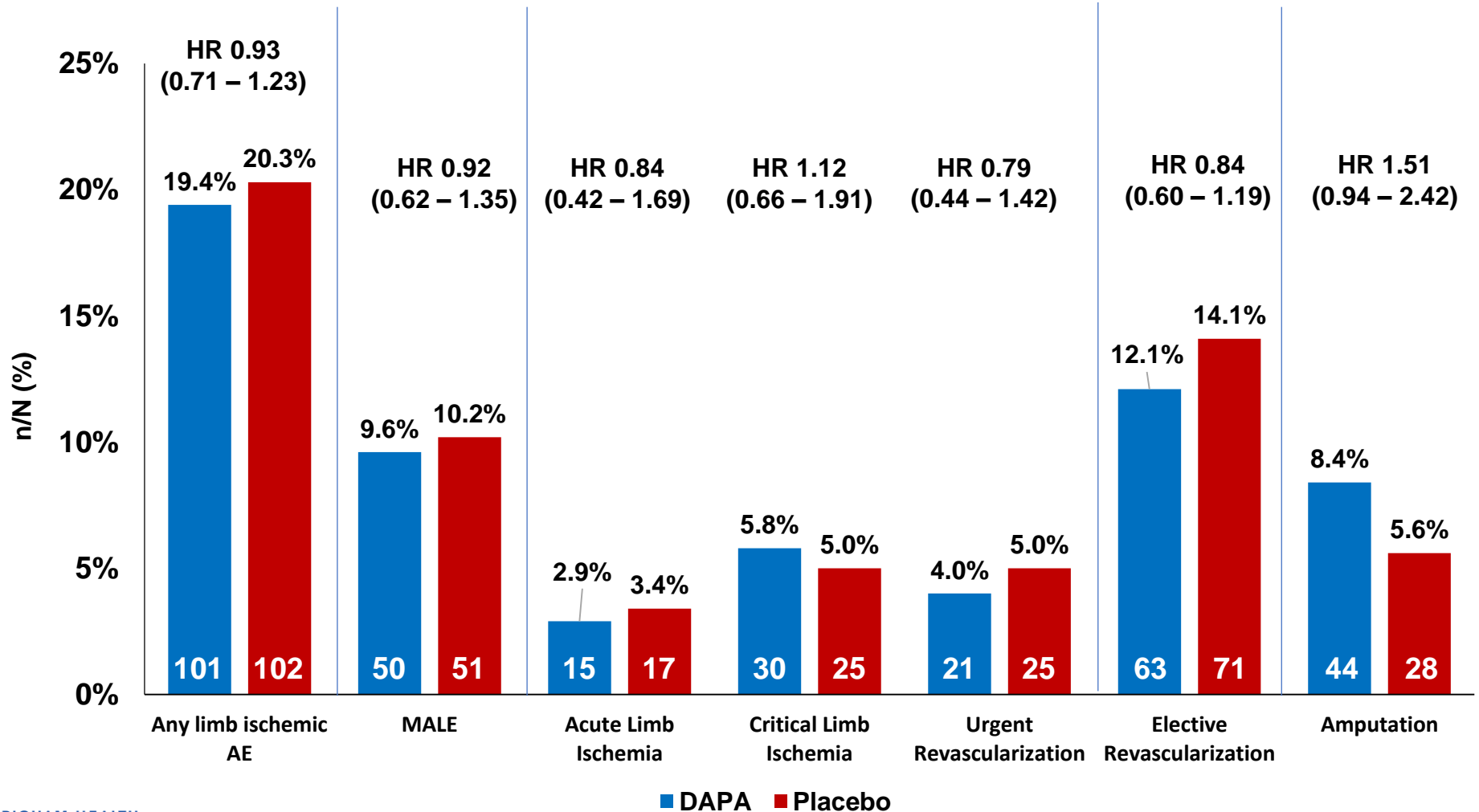
Dapagliflozin and Limb Outcomes

PAD Patients



DECLARE
 TIMI-58
TIMI STUDY GROUP/HADASSAH MEDICAL ORG
 Dapagliflozin Effect on Cardiovascular Events

N=1025 **All p-values > 0.05**



MALE Defined as ALI, CLI, amputation for ischemia or Urgent Revascularization for Ischemia

- 1. Patients with PAD were at heightened risk of cardiac, renal and limb complications vs. those without**
- 2. The efficacy of dapagliflozin for CVD/HF and renal outcomes was consistent regardless of PAD status but with greater absolute benefits in PAD**
- 3. There was no significant excess risk of amputations or limb ischemic events with dapagliflozin in the overall population**
- 4. There was no consistent pattern of risk or benefit related to limb events in patients with PAD or other high-risk subgroups**