Dewilde WJM et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. The Lancet 2013

Clinical question posed by this trial: In patients with long-term indication for oral anticoagulant (OAC) and require percutaneous coronary intervention, how does double therapy (OAC + clopidogrel) compare with triple therapy (OAC + clopidogrel + ASA) in terms of bleeding and thrombotic events?

Context:

- Many patients with A. Fib, mechanical or bio-prosthetic heart valves or venous thrombosis require long-term treatment with OAC (eg. warfarin)
- Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor is the standard of care following stent implantation
- Data with bare-metal stents (BMS) have demonstrated superiority of DAPT to warfarin plus aspirin[1]
- Observational studies suggest that in patients with A. Fib after stent placement, triple therapy reduces CV events compared to DAPT but at the expense of more bleeds
- Triple therapy also increases the risk of major bleeding events without significantly reducing thromboembolic events compared to single antiplatelet therapy + warfarin [2,3]

Methodology

Study design	Open label, MC, RCT x 1 year
Sequence generation	Appropriate (computer-generated) • Stratified by centre ("blocked randomization per centre")
Allocation concealment	Adequate (sequentially numbered sealed envelopes and allocated by secretarial staff of the research department of each centre)
Blinding	• Open label (no placebo in double therapy group) • All events adjudicated by clinical events committee unaware of treatment allocations
Loss to follow-up	98.3% follow up (1 person lost to follow up in each group)
Population analyzed	Modified intention-to-treat (included all who received study drugs, not all randomized patients)
Intervention	• OAC (INR = 2.0) + clopidogrel 75mg po daily • OAC (INR = 2.0) + clopidogrel 75mg po daily + ASA 80-100mg po daily
Outcomes	• **Any bleeding (TIMI, GUSTO, BARC)** • Composite of death, MI, stroke, target vessel revascularization, stent thrombosis • Death • MI • Stroke • Target vessel revascularization • Stent thrombosis
Funding	• Not industry funded • Antonius Ziekenhuis Foundation • Strect Foundation

Participants

Setting	15 centres (Belgium and Netherlands)
Inclusion criteria	• 18-80 years old • Indication for long-term OAC • Severe coronary lesion with indication for PCI
Relevant exclusion criteria	• History of intracranial bleeding • Cardiogenic shock • Contraindication to study drugs • Peptic ulcer ≤ 6 months • Thrombocytopenia (< 50 x 10^9/L) • Major bleeding ≤ 12 months • Pregnancy
Study size	• 573 patients randomized ○ 563 patients included in ITT analysis
"Average" patient	• Male 77-82% • Age ~70 years old • Comorbidities ○ Diabetes 25% ○ HTN 70% ○ Hypercholesterolemia 70% ○ History of MI 35% ○ History of stroke 18% ○ History of heart failure 25% ○ History of renal failure 18% ○ History of PCI 35% ○ History of GI bleed 5% ○ Positive FmHx 42% • Indication for OAC - Afib/flutter 70% - Mechanical valve 10% - Other 20% • Meds on admission - Beta blocker 78% - ACEI/ARB 67% - Statin 70 vs 80% - PPI use 35% • CHADS score - 2 (32 vs 26%) - 3 (32 vs 36 %) - 4 (16 vs 15%) - >5 (1 vs 2%) • Stent type - BMS (32 vs 30%) - DES (65 vs 64%) - BMS and DES (1 vs 4%) - Radial access (26%) and femoral access (74%) - LAD (41%) and RCA (27%)
Clinically-relevant baseline differences (DT vs TT)	• Smoker (22 vs 15%)

Results				
Outcomes	Double therapy (n=279)	Triple therapy (n-284)	Hazard ratio	Absolute risk reduction
All-cause mortality	7 (2.5%)	18 (6.3%)	0.39 (0.16-0.93)	**3.8%**
Composite	31 (11.1%)	50 (17.6%)	0.60 (0.38-0.94)	**6.5%**
MI	9 (3.2%)	13 (4.6%)	0.69 (0.29-1.6)	1.4%
Stroke	3 (1.1%)	8 (2.8%)	0.37 (0.10-1.4)	5%
Stent thrombosis	4 (1.4%)	9 (3.2%)	0.44 (0.14-1.44)	1.8%
Any bleeding event	54 (19.4%)	126 (44.4%)	0.36 (0.26-0.50)	**25%**
Major TIMI Bleed	9 (3.2%)	16 (5.6%)	0.56 (0.25-1.27)	2.4%
Severe GUSTO Bleed	4 (1.4%)	10 (3.5%)	0.40 (0.12-1.27)	2.1%
Any transfusions	11 (3.9)	27 (9.5%)	0.39 (0.17-0.84)	5.6%

Major Limitations

Design

- Open label design leading to potential for bias
- No information on TTR for OAC (extrapolated from RELY trial where TTR was ~70% and patients were being monitored by specialized thrombosis service)

Results

- ASA continued in only 66% of triple therapy group.

Generalizability

- Done in Europe
- Excluded patients with ICH and recent major bleeding
- Can't apply this data directly to patients on new oral anticoagulants (NOACs)
    - In ATLAS ACS 2-TIMI 51,[4] patients without an indication for oral anticoagulation and with a low risk of bleeding, had a reduced risk of death and CV events but an increase in major bleed with *tiny* doses of rivaroxaban (2.5 mg BID)
    - Trials of other oral anticoagulants are not as positive.[5]

Conclusions:

- Triple therapy significantly increases the risk of bleeding compared to double therapy of OAC + clopidogrel
- This study showed a mortality benefit with double therapy compared to triple therapy
    - Mortality was a secondary outcome, so the result is less reliable
    - This data can't be applied to patients on NOACs

[1] Cardiology 2005, 104:101-6
[2] Chest. 2011;139:260-70.
[3] Circulation. 2012;126:1185-1193
[4] NEJM. 2012;366:9-19.
[5] Arch Intern Med. 2012;172:1537-45.