Update Triple Therapie
Was und wie lange?
1. **Valvuläre, hypertensive und koronare Herzkrankheit**

- Koronarangiographie bei akutem infero-posterioren Myokardinfarkt 03/2000: PTCA der RCX. Signifikante Stenose des RIVA.
- Re-Koronarangiographie 05/2000: erfolgreiche PTCA und Stenteinlage am proximalen RIVA
- TTE 10/2015: LVEF ca. 40%, mittelschwere funktionelle Mitralklappeninsuffizienz
- kvRF: art. Hypertonie, Hypercholesterinämie, positive Familienanamnese

**Aktuell:**

- kardiale Dekompensation bei Mitralklappeninsuffizienz und Vorhofflimmern
- TTE 31.07.2017: linker Ventrikel normal dimensioniert, LVEF 40%, Akinesie inferior-/inferolateral. Mittelschwere bis beginnend schwergradige, funktionelle Mitralinsuffizienz bei Tethering des posterioren Segels mit systolischem Rückfluss in die Pulmonalvenen (EROA 0.22 cm² bei PISA von 0.7cm, E 0.9 m/s)
- TTE vom 08.08.2017 nach Rekompensation: stationärer Befund, kein erhöhter sPAP mehr
- Koro vom 07.08.2017: gutes Ergebnis nach Stenting RCX und RIVA. Seriell hochgradig stenosierte ACD. Normale pulmonale Druckwerte und Widerstände (mPA 24mmHg, mPCWP 10 mmHg)
- Rotablation der ACD im Verlauf geplant
U.K., 1939

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<th>Paroxysmales Vorhofflimmern, ED 03.08.2017</th>
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<td>Aktuell: Beginn Eliquis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>3.</th>
<th>Thrombozytopenie seit 04/16 DD ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Folsäure, Vitamin B12: normwertig (08/17)</td>
</tr>
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<td></td>
<td>Aktuell:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4.</th>
<th>Chronische Niereninsuffizienz KDIGO Stadium 2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>- eGFR (CKD-EPI) 63ml/min (07.08.2017)</td>
</tr>
<tr>
<td></td>
<td>Aktuell:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5.</th>
<th>Subtotale Blasenhalssklerose und kleines Rezidiv-Prostataadenom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Restharnmengen bis 500 ml</td>
</tr>
<tr>
<td></td>
<td>- Prostatasyndrom Stadium III mit Retentionsblase</td>
</tr>
<tr>
<td></td>
<td>- TUR-Prostata (monopolar), Zystostomieeinlage und retrograde Ureteropyelographie rechts am 15.06.2016 und Re-TUR-Prostata bei Rezidivadenom am 05.10.2016</td>
</tr>
<tr>
<td></td>
<td>- drahtgeführte DK-Einlage am 23.02.2017</td>
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<tr>
<td></td>
<td>- TUR-Blasenhalsinzision, TUR-P und Zystostomie-Einlage am 24.03.2017</td>
</tr>
<tr>
<td></td>
<td>Aktuell:</td>
</tr>
</tbody>
</table>
Rotablation mit Stent-Implantation
Dilemma

• Patients with atrial fibrillation and Stent-Implantation
  – warfarin better than dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin for the prevention of stroke\(^1\)
  – DAPT better than aspirin plus warfarin for the prevention of stent thrombosis\(^2\)

Challenge of triple therapy: Bleeding

Atrial fibrillation and Percutaneous coronary intervention: Six questions

1. How common is CAD (and PCI) in Afib patients?
2. Can beneficial effects of NOAC vs Warfarin in AFib patients be adapted/extended to Afib and CAD?
3. Can aspirin be eliminated from triple therapy?
4. Efficacy of new strategy for the prevention of stroke or stent thrombosis?
5. Do we need certain Individualization or one size fits all? Use lower dose of NOACs in combination with ASS and/or Clopidogrel?
6. Combination of Ticagrelor or Prasugrel with (N)OACs allowed?
Overlap between nonischemic heart failure (NIHF), ischemic heart failure (IHF), coronary artery disease (CAD), and atrial fibrillation/flutter (AF) cohorts.

AF as a comorbid condition

AF is common in CAD (1/3)

Apixaban in patients with atrial fibrillation and prior coronary artery disease: NOACs better than VKA?

- similar effects of apixaban among patients with and without prior CAD on reducing stroke or systemic embolism and death from any cause
- Less bleedings with NOACs
- ¼ of patients with AF enrolled in ARISTOTLE had prior PCI

Overall: Beneficial effects of NOAC vs Warfarin in AFib patients with CAD

Trials investigating dual (triple) therapy according to size and type of investigated population

European Heart Journal (Update on DAPT) 2017
The WOEST trial: Is ASA Necessary in Triple Therapy (with VKA)?

Small-scale, open-label WOEST study (N=573) compared safety outcomes with triple therapy (VKA plus clopidogrel plus ASA) vs dual therapy (VKA plus clopidogrel): 69% of WOEST patients had AF.

Use of dual therapy was associated with significantly lower rates of bleeding and overall mortality vs triple therapy, with similar rates of thrombotic events.

\[ p < 0.05 \]

**PIONEER AF-PCI Study Design**

**Design:** An open-label, randomized, controlled phase IIIb safety study

**Population:** patients with paroxysmal, persistent or permanent NVAF undergoing PCI (with stent placement)

**Decision for DAPT duration:** 1, 6 or 12 months

- Rivaroxaban 15 mg OD*# plus single antiplatelet‡
- Rivaroxaban 2.5 mg BID# plus DAPT§
- Rivaroxaban 15 mg OD* plus low-dose ASA
- VKA (INR 2.0–3.0)¶ plus DAPT§

**DAPT duration (1 or 6 months)**

**End of treatment (12 months)**

---

*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); †first dose 12–72 hours after sheath removal

**PIONEER AF-PCI**

**Study Flow**

- 2,236 screened
- 112 not eligible
- 2,124 enrolled

- **709** randomized to Group 1
  - 696 received ≥1 dose
    - No DAPT stratification
  - **696** in safety analysis
    - **694** in efficacy analysis*

- **709** randomized to Group 2
  - 706 received ≥1 dose
    - 1 month DAPT: 108
    - 6 months DAPT: 248
    - 12 months DAPT: 350
  - **706** in safety analysis
    - **704** in efficacy analysis*

- **706** randomized to Group 3
  - 697 received ≥1 dose
    - 1 month DAPT: 113
    - 6 months DAPT: 243
    - 12 months DAPT: 341
  - **697** in safety analysis
    - **695** in efficacy analysis*

---

*Some patients excluded due to site violation of GCP guideline; no patients were lost to follow-up

## Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 Rivaroxaban 15 mg OD plus single antiplatelet (N=709)</th>
<th>Group 2 Rivaroxaban 2.5 mg BID plus DAPT (N=709)</th>
<th>Group 3 VKA plus DAPT (N=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>70.4±9.1</td>
<td>70.0±9.1</td>
<td>69.9±8.7</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>181 (25.5)</td>
<td>174 (24.5)</td>
<td>188 (26.6)</td>
</tr>
<tr>
<td>CrCl, ml/min, mean ± SD</td>
<td>78.3±31.3</td>
<td>77.5±31.8</td>
<td>80.7±30.0</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score, mean ± SD*</td>
<td>3.73±1.69</td>
<td>3.78±1.62</td>
<td>3.82±1.55</td>
</tr>
<tr>
<td>HAS-BLED score, mean ± SD*</td>
<td>3.00±0.91</td>
<td>2.92±0.96</td>
<td>2.99±0.91</td>
</tr>
<tr>
<td>Urgency of revascularization, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>428 (60.4)</td>
<td>430 (60.6)</td>
<td>449 (63.6)</td>
</tr>
<tr>
<td>Urgent</td>
<td>281 (39.6)</td>
<td>279 (39.4)</td>
<td>257 (36.4)</td>
</tr>
<tr>
<td>Type of index event, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>130 (18.5)</td>
<td>129 (18.4)</td>
<td>123 (17.8)</td>
</tr>
<tr>
<td>STEMI</td>
<td>86 (12.3)</td>
<td>97 (13.8)</td>
<td>74 (10.7)</td>
</tr>
<tr>
<td>UA</td>
<td>145 (20.7)</td>
<td>148 (21.1)</td>
<td>164 (23.7)</td>
</tr>
<tr>
<td>P2Y₁₂ inhibitor at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>660 (93.1)</td>
<td>664 (93.7)</td>
<td>680 (96.3)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>12 (1.7)</td>
<td>11 (1.6)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>37 (5.2)</td>
<td>34 (4.8)</td>
<td>21 (3.0)</td>
</tr>
</tbody>
</table>

No Differences Between Groups

*Values calculated from data in published manuscript (not explicitly stated)
Both Rivaroxaban Strategies Associated With Significantly Improved Safety

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); \( p<0.001 \)
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); \( p<0.001 \)

ISTH Major Bleeding Significantly Reduced with Rivaroxaban Strategies vs VKA

Both rivaroxaban strategies associated with significant reduction in ISTH major and clinically relevant non-major bleeding vs the VKA plus DAPT strategy

Incidence of fatal bleeding: 0.3% in group 1, 0.3% in group 2, 0.9% in group 3

Similar Efficacy Between All Three Treatment Strategies*

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); p=0.750
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); p=0.765

*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints

PIONEER AF-PCI
Limitations

**Power**
- Trial was not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints
  - Power to detect a ≥15% risk reduction for major adverse CV events was 11.4%
  - Assuming a 90% power to detect a 15% relative difference between the treatment groups, a superiority trial would require 13,598 participants/arm

**DAPT stratification**
- Stratification of patients in Groups 2 and 3 according to duration of DAPT (1, 6 or 12 months) was determined by the attending physician
  - This resulted in imbalances in patient characteristics between treatment strategies within each stratum

Discussion: Afib and PCI

- Elimination of aspirin from triple therapy or the use of very-low-dose rivaroxaban with DAPT is safe.

- Efficacy of these strategies for the prevention of stroke or stent thrombosis is still uncertain.

- «….elimination of aspirin from triple therapy could be associated with a 25% increase in the risk of stent thrombosis, but this trial does not have the power to assess this outcome….”

Future: Major Randomized Trials Comparing Anticoagulation Strategies for Patients with Atrial Fibrillation Undergoing PCI.

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Participants</th>
<th>Control</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>ClinicalTrials.gov No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUAL-PCI</td>
<td>2800</td>
<td>Aspirin, P2Y\textsubscript{12} inhibitor, and vitamin K antagonist</td>
<td>Dabigatran (either 110 mg twice daily or 150 mg twice daily) plus P2Y\textsubscript{12} inhibitor</td>
<td>Major bleeding and clinically relevant nonmajor bleeding, defined according to ISTH criteria</td>
<td>NCT02164864</td>
</tr>
<tr>
<td>ENTRUST-AF-PCI</td>
<td>1500</td>
<td>Aspirin, P2Y\textsubscript{12} inhibitor, and vitamin K antagonist</td>
<td>Edoxaban (60 mg once daily) plus P2Y\textsubscript{12} inhibitor</td>
<td>Major bleeding and clinically relevant nonmajor bleeding, defined according to ISTH criteria</td>
<td>NCT02866175</td>
</tr>
<tr>
<td>AUGUSTUS</td>
<td>4600</td>
<td>Either aspirin or vitamin K antagonist (2-by-2 factorial design)</td>
<td>Either apixaban (5 mg twice daily) or placebo</td>
<td>Major bleeding and clinically relevant nonmajor bleeding, defined according to ISTH criteria</td>
<td>NCT02415400</td>
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* The REDUAL-PCI trial is the Evaluation of Dual Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Atrial Fibrillation That Undergo a PCI with Stenting; the ENTRUST-AF-PCI trial is Edoxaban Treatment versus Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; and the AUGUSTUS trial is A Study of Apixaban in Patients with Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart. ISTH denotes International Society on Thrombosis and Haemostasis, and PCI percutaneous coronary intervention.

“….these trials are not designed to assess ischemic outcomes; they target bleeding…..”

Atrial fibrillation and Percutaneous coronary intervention: Six questions

1. How common is CAD (and PCI) in Afib patients?

2. Can beneficial effects of NOAC vs Warfarin in AFib patients be adapted/extended to Afib and CAD?

3. Can aspirin be eliminated from triple therapy?

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5. Do we need certain Individualization or one size fits all? Use lower dose of NOACs in combination with ASS and/or Clopidogrel

6. Combination of Ticagrelor or Prasugrel with (N)OACs allowed?
Atrial fibrillation and Percutaneous coronary intervention: Eight points to keep in mind

1. AF is common in CAD (1/3), PCI in elderly (Afib) pts is common
2. Beneficial effects of NOAC vs Warfarin in Afib patients with CAD
3. Tightrope walk between prevention of stent thrombosis and stroke
4. Elimination of aspirin from triple therapy or the use of very-low-dose rivaroxaban with DAPT is safe
5. Efficacy of these strategies for the prevention of stroke or stent thrombosis is still uncertain
6. Individualizing (triple) therapy on the basis of a patient’s risk for bleeding and stent thrombosis until the results of larger trials are available
7. Use lower dose of NOACs in combination with ASS and/or Clopidogrel!
8. Do not combine Ticagrelor oder Prasugrel with (N)OACs!
2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Marco Valgimigli* (Chairperson) (Switzerland), Héctor Bueno (Spain), Robert A. Byrne (Germany), Jean-Philippe Collet (France), Francesco Costa (Italy), Anders Jeppsson¹ (Sweden), Peter Jüni (Canada), Adnan Kastrati (Germany), Philippe Kolh (Belgium), Laura Mauri (USA), Gilles Montalescot (France), Franz-Josef Neumann (Germany), Mate Petricevic¹ (Croatia), Marco Roffi (Switzerland), Philippe Gabriel Steg (France), Stephan Windecker (Switzerland), and Jose Luis Zamorano (Spain)

Additional Contributor: Glenn N. Levine (USA)
What is new in the 2017 ESC focussed update on DAPT?

**Change in recommendations**

**Before → 2017**
- Pretreatment with P2Y₁₂ inhibitors when PCI is planned
- Liberal use of PPI to mitigate GI bleeding risk
- Elective surgery requiring discontinuation of the P2Y₁₂ inhibitor after 1 month
- Ticagrelor interruption of 3 days prior elective surgery
- Dual therapy as an alternative to triple therapy when bleeding risk outweighs the ischaemic risk
- Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.
- Routine platelet function testing to adjust therapy

**New recommendations 2017**
- The occurrence of actionable bleeding while on DAPT should prompt reconsideration of type and duration of DAPT regimen.
- The decision for DAPT duration should be dynamic and reassessed during the course of the initially selected DAPT regimen.
- Discontinuation of P2Y₁₂ inhibitor therapy after 6 months when stenting ACS patients with PRECISE-DAPT ≥ 25
- 6-month DAPT regimen in patients with SCAD treated with drug-coated balloon
- Early administration of ticagrelor/doripenem in NSTE-ACS with invasive approach
- Ticagrelor 60 mg b.i.d preferred over other oral P2Y₁₂ inhibitors for DAPT continuation >12 months in post-MI

**New/revised concepts**
- Metallic stent and DAPT duration
  - Switch between P2Y₁₂ inhibitors
    - Risk scores to guide DAPT duration
      - PRECISE DAPT score
      - DAPT score
    - Specific profiling
      - Definition of complex PCI
      - Unfavourable profile for OAC and APT
      - Gender considerations and special populations
  - DAPT duration without stenting
    - Medical management
    - CABG or cardiac surgery
  - Anticoagulation and DAPT
    - Acute and chronic setting
    - Dosing regimen

ACS = acute coronary syndrome; APT = anti-platelet therapy; CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NSTE= Non-st-segment elevation; OAC = oral anti-coagulant; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; Stable CAD = stable coronary artery disease.
U.K., 1939

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- Rotablation der ACD im Verlauf geplant

Mehrere Stents, lange Läsion, diffuse 3-Gefäß-Erkrankung
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</tr>
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Management von Patienten mit perkutaner koronarer Intervention (PCI) und Notwendigkeit einer oralen Antikoagulation bei nicht-valvulärem Vorhofflimmern

CHA₂DS₂-VASc ≤ 1  

CHA₂DS₂-VASc ≥ 2

HAS-BLED ≥ 3

HAS-BLED ≤ 2

(D)OAK* + DAPT für 1 Monat dann (D)OAK + SAPT (6-) 12 Monate

(D)OAK* + DAPT für (3-)6 Monate dann (D)OAK + SAPT bis zu 12 Monate

(D)OAK* + Clopidogrel bis 12 Monate

Legende:
DAPT: Duale Anti-Plättchen-Therapie (ASS 100 mg und Clopidogrel)
SAPT: Singuläre Anti-Plättchen-Therapie (i.d.Regel Clopidogrel)
(D)OAK-Dosierung reduzieren bei Triple-Therapie, d.h. 2 x 110 mg Dabigatran/d, 15 mg Rivaroxaban/d, 2 x 2.5 mg Apixaban/d
SKHK: stabile koronare Herz-Krankheit
HAS-BLED siehe Seite 239 CHA₂DS₂-VASc siehe Seite 237

### High-risk features of stent-driven recurrent ischaemic events

- Prior stent thrombosis on adequate antiplatelet therapy.
- Stenting of the last remaining patent coronary artery.
- Diffuse multivessel disease especially in diabetic patients.
- Chronic kidney disease (i.e. creatinine clearance <60 mL/min).
- At least three stents implanted.
- At least three lesions treated.
- Bifurcation with two stents implanted.
- Total stent length >60 mm.
- Treatment of a chronic total occlusion.
Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)