Use of Direct Oral Anticoagulants in Triple Therapy

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PGY1 Resident

Pharmacy Grand Rounds
December 18th, 2018
Objectives

Review recommendations for triple therapy, including length of triple therapy in patients with atrial fibrillation undergoing coronary stent procedures

Identify risk and benefits of DOACs in patients with atrial fibrillation undergoing coronary stent procedures

Discuss limitations of studies describing use of DOACs compared to warfarin in patients with atrial fibrillation undergoing coronary stent procedures
Definitions

ACS – Acute coronary syndrome
ACC – American College of Cardiology
AHA – American Heart Association
ASA – Aspirin
BMS – Bare metal stent
DAPT – Dual antiplatelet therapy (P2Y12 inhibitor plus ASA)
DES – Drug eluting stent
DOAC – Direct oral anticoagulant
NSTE – Non-ST elevation
PCI – Percutaneous intervention
TTR – Time in therapeutic range
VKA – Vitamin K antagonist
Background

Approximately 5% of patients w/ atrial fibrillation undergo a PCI

DAPT superior to oral anticoagulation in reducing risk of thrombosis in patients undergoing coronary stent placement

Oral anticoagulation superior to DAPT in reducing ischemic stroke with atrial fibrillation

Triple therapy increases risk of major bleeds:
  • 2.2% in the first month
  • 4% to 12% in the first year

Guidelines
2012 CHEST Guideline for Antithrombotic Therapy for Atrial Fibrillation

Triple therapy favored over DAPT:
- One month for BMS
- 3 to 6 months after DES

After initial period:
- VKA therapy plus single antiplatelet therapy

After 12 months:
- VKA monotherapy

2014 ACC/AHA NSTE-ACS Guideline

No mention of DOACs in patients requiring triple therapy

2016 update on duration of dual antiplatelet therapy refers back to this guideline


2018 CHEST Guideline for Antithrombotic Therapy for Atrial Fibrillation

Compared to the 2012 guidelines:
- Differentiates between type of procedure and bleed risk
  - Procedure:
    - Elective versus ACS
  - Bleed risk:
    - Low
    - High

## 2018 CHEST Guideline for Antithrombotic Therapy for Atrial Fibrillation

- **Bleed risk based on HAS-BLED score:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Examples</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Uncontrolled, &gt;160 mmHg systolic</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>Dialysis, SCr &gt; 2.26 mg/dL</td>
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</table>
Elective coronary stent procedures with low bleed risk

Triple therapy favored over DAPT for 1 to 3 months

Anticoagulation monotherapy

Anticoagulation plus clopidogrel until 12 months

Elective coronary stent procedures with high bleed risk

Triple therapy for 1 month

Anticoagulation monotherapy

Anticoagulation plus clopidogrel for 6 months

Coronary stent procedures for ACS with low bleed risk

- **Triple therapy** for 6 months
  - Anticoagulation
  - Plus clopidogrel

- **Anticoagulation monotherapy** until 12 months

Coronary stent procedures for ACS with high bleed risk

- Triple therapy for 1 to 3 months
- Anticoagulation monotherapy

- Anticoagulation plus clopidogrel up to 12 months

Patient case

BT is a 67 year old male presenting to the emergency department from an outside hospital with complaints of:

- Shortness of breath
- Chest pain
Patient case

Patient case

• Past medical history
  Hypertension
  Atrial fibrillation
  Type 2 diabetes
  Depression
  Systolic heart failure

• Social history
  Smoker
    • 1 pack per day
  No alcohol use

• Medications
  Losartan
  Warfarin
  Metformin
  Glipizide
  Insulin glargine
  Fluoxetine
  Furosemide
  Metoprolol succinate
  Atorvastatin
Patient case

• Vital Signs
  Temp: 37° C
  BP: 150/80 mm Hg
  Respirations: 18 per min.
  95% O₂ sat on room air
  HR: 101 beats/min.

• Labs
  Hgb: 12.4 mg/dL
  Platelets: 176
  INR: 2.5 (TTR > 75%)
  EtOH: < 10
  ALT: 54
  AST: 32
  Serum creatinine: 0.76
Patient case

BT is taken immediately to the cath lab for an angiogram and has two stents placed. No history of stroke, major bleeding episodes or abnormal liver or kidney function. How long should he receive triple therapy:

A. 1 month
B. 3 months
C. 6 months
D. 12 months
## HAS-BLED

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Patient case – Question #1

• BT is taken **immediately** to the cath lab for an angiogram and has two stents placed. No history of stroke, major bleeding episodes or abnormal liver or kidney function. How long should he receive triple therapy:
  • 1 month
  • 3 months
  • 6 months
  • 12 months
Summary

2018 CHEST guidelines show no preference between warfarin and DOACs

Length of triple, dual, and monotherapy determined by:

1. Type of procedure
2. Bleed risk
Risks and benefits of DOACs in triple therapy
Risks and benefits of DOACs in triple therapy

• Three studies have looked at this:
  • PIONEER AF-PCI
  • RE-DUAL PCI
  • Direct oral anticoagulants versus standard triple therapy in atrial fibrillation and PCI: meta-analysis
PIONEER AF-PCI background

Multicenter, randomized, open label trial

2124 patients with nonvalvular atrial fibrillation who had undergone PCI with stenting

Goals of study:

• To determine the safety and effectiveness of rivaroxaban when either one or two antiplatelet agents are used

• Primary outcome: significant bleeding

# PIONEER AF-PCI

**Randomized 1:1:1 to receive:**

<table>
<thead>
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<th>Treatment</th>
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<tbody>
<tr>
<td>Rivaroxaban 15 mg daily plus P2Y$_{12}$</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg twice daily plus DAPT</td>
</tr>
<tr>
<td>VKA plus DAPT</td>
</tr>
</tbody>
</table>

Rivaroxaban 15 mg daily plus P2Y$_{12}$
- WOEST trial

Rivaroxaban 2.5 mg twice daily plus DAPT
- ATLAS ACS 2-TIMI 51 trial


# PIONEER AF-PCI results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Group 1 vs 3</th>
<th>Group 2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant bleeding</td>
<td>HR=0.59; p&lt;0.001</td>
<td>HR=0.63; p&lt;0.001</td>
</tr>
<tr>
<td>Bleeds requiring medical attention</td>
<td>HR=0.61; p&lt;0.001</td>
<td>HR=0.67; p=0.002</td>
</tr>
<tr>
<td>Major adverse cardiovascular event</td>
<td>HR=1.08; p=0.75</td>
<td>HR=0.93; p=0.76</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>HR=1.20; p=0.79</td>
<td>HR=1.44; p=0.57</td>
</tr>
</tbody>
</table>

# PIONEER AF-PCI

<table>
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<th>Limitations</th>
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<tbody>
<tr>
<td>20% drop out rate</td>
</tr>
<tr>
<td>Inadequately powered</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg dose not indicated</td>
</tr>
<tr>
<td>DAPT duration was determined by clinician</td>
</tr>
<tr>
<td>Patient characteristics were imbalanced</td>
</tr>
</tbody>
</table>

RE-DUAL PCI background

Multi-center, randomized, open-label trial

2725 patients with nonvalvular atrial fibrillation who had undergone PCI

Goals of study:

• To compare DOAC to VKA in patients requiring triple therapy, and whether the omission of aspirin reduced the risk of bleeding

• Primary outcome: first major or clinically significant bleeding event

### RE-DUAL PCI

All patients in the United States and under the age of 70 years old were randomized:

<table>
<thead>
<tr>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin plus DAPT</td>
</tr>
<tr>
<td>Dabigatran 110 mg twice daily plus P2Y12 inhibitor</td>
</tr>
<tr>
<td>Dabigatran 150 mg twice daily plus P2Y12 inhibitor</td>
</tr>
</tbody>
</table>

Elderly patients outside the United States:

<table>
<thead>
<tr>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin plus DAPT</td>
</tr>
<tr>
<td>Dabigatran 110 mg twice daily plus P2Y12 inhibitor</td>
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</tbody>
</table>

## RE-DUAL PCI results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Dabigatran 110 mg vs Standard triple therapy</th>
<th>Dabigatran 150 mg vs Standard triple therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st major or clinically relevant non-major bleed</td>
<td>HR=0.52; p&lt;0.001</td>
<td>HR=0.72; p&lt;0.002</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>HR=0.52; p&lt;0.001</td>
<td>HR=0.64; p=0.02</td>
</tr>
<tr>
<td>Total bleeding</td>
<td>HR=0.54; p&lt;0.001</td>
<td>HR=0.72; p&lt;0.001</td>
</tr>
<tr>
<td>Composite efficacy end point</td>
<td>HR=1.13; p=0.30</td>
<td>HR=0.89; p=0.44</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>HR=1.86; p=0.15</td>
<td>HR=0.99; p=0.98</td>
</tr>
<tr>
<td>Stroke</td>
<td>HR=1.30; p=0.48</td>
<td>HR=1.09; p=0.85</td>
</tr>
</tbody>
</table>

## RE-DUAL PCI results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Combined dabigatran dual therapy vs standard triple therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite efficacy end point</td>
<td>HR=1.04; p=0.74</td>
</tr>
<tr>
<td></td>
<td>p=0.005 for non-inferiority</td>
</tr>
<tr>
<td>Thromboembolic events or death</td>
<td>HR=1.17; p=0.25</td>
</tr>
<tr>
<td></td>
<td>p=0.11 for non-inferiority</td>
</tr>
</tbody>
</table>

RE-DUAL PCI

<table>
<thead>
<tr>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol amended</td>
</tr>
<tr>
<td>Inadequately powered</td>
</tr>
<tr>
<td>Composite end point that combined both dabigatran doses</td>
</tr>
<tr>
<td>Dabigatran plus P2Y12 compared to standard triple therapy</td>
</tr>
</tbody>
</table>

Meta-analysis background

Identified 34 trials with 21 that were eligible
  • 2 were deemed appropriate
4849 total patients
  • Rivaroxaban or dabigatran plus one or two antiplatelet agents compared to standard triple therapy
Relative risks calculated to allow for pooling

Goal of study:
  • Determine safety and efficacy of DOACs in combination with antiplatelet agents post PCI

## Meta-analysis results

<table>
<thead>
<tr>
<th>End Point</th>
<th>DOAC vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bleeding</td>
<td>RR=0.66; p&lt;0.00001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>RR=0.59; p&lt;0.00001</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>RR=1.03; p=0.69</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RR=1.09; p=0.57</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>RR=1.46; p=0.16</td>
</tr>
</tbody>
</table>

## Limitations

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Two different DOACs compared</td>
</tr>
<tr>
<td>Dual therapy vs triple therapy</td>
</tr>
<tr>
<td>Follow up periods were different</td>
</tr>
<tr>
<td>Mortality data not used</td>
</tr>
</tbody>
</table>

Question #2

• When a DOAC plus antiplatelet agent(s) was compared to standard triple therapy which of the following is true:
  1. More bleeding but equivalent efficacy
  2. Equivalent bleeding and efficacy
  3. Equivalent bleeding and improved efficacy
  4. Less bleeding and equivalent efficacy
  5. Less bleeding and improved efficacy
Question #2

• When a DOAC plus antiplatelet agent(s) was compared to standard triple therapy which of the following is true:
  1. More bleeding but equivalent efficacy
  2. Equivalent bleeding and efficacy
  3. Equivalent bleeding and improved efficacy
  4. Less bleeding and equivalent efficacy
  5. Less bleeding and improved efficacy
Question #3

- Which of the following is NOT a limitation of the studies comparing DOACs to warfarin in patients with atrial fibrillation that are undergoing coronary stent procedures:
  1. DOAC dosing
  2. Initial randomization
  3. Dual vs triple therapy
  4. Type 1 error
  5. High drop out rate
Question #3

• Which of the following is NOT a limitation of the studies comparing DOACs to warfarin in patients with atrial fibrillation that are undergoing coronary stent procedures:

1. DOAC dosing
2. Initial randomization
3. Dual vs triple therapy
4. Type 1 error
5. High drop out rate
Ask Mayo Expert

- Warfarin currently the only oral anticoagulant indicated for patients with a myocardial infarction
Summary

Patients requiring triple therapy have a heightened risk of bleeding

2018 CHEST guidelines have promoted DOACs use in triple therapy

Early studies are promising, but overall quantity of studies is lacking

- Apixaban and edoxaban not studied
Objectives

Review recommendations for triple therapy, including length of triple therapy in patients with atrial fibrillation undergoing coronary stent procedures.

Identify risk and benefits of DOACs in patients with atrial fibrillation undergoing coronary stent procedures.

Discuss limitations of studies describing the use of DOACs compared to warfarin in patients with atrial fibrillation undergoing coronary stent procedures.
Use of Direct Oral Anticoagulants in Triple Therapy

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