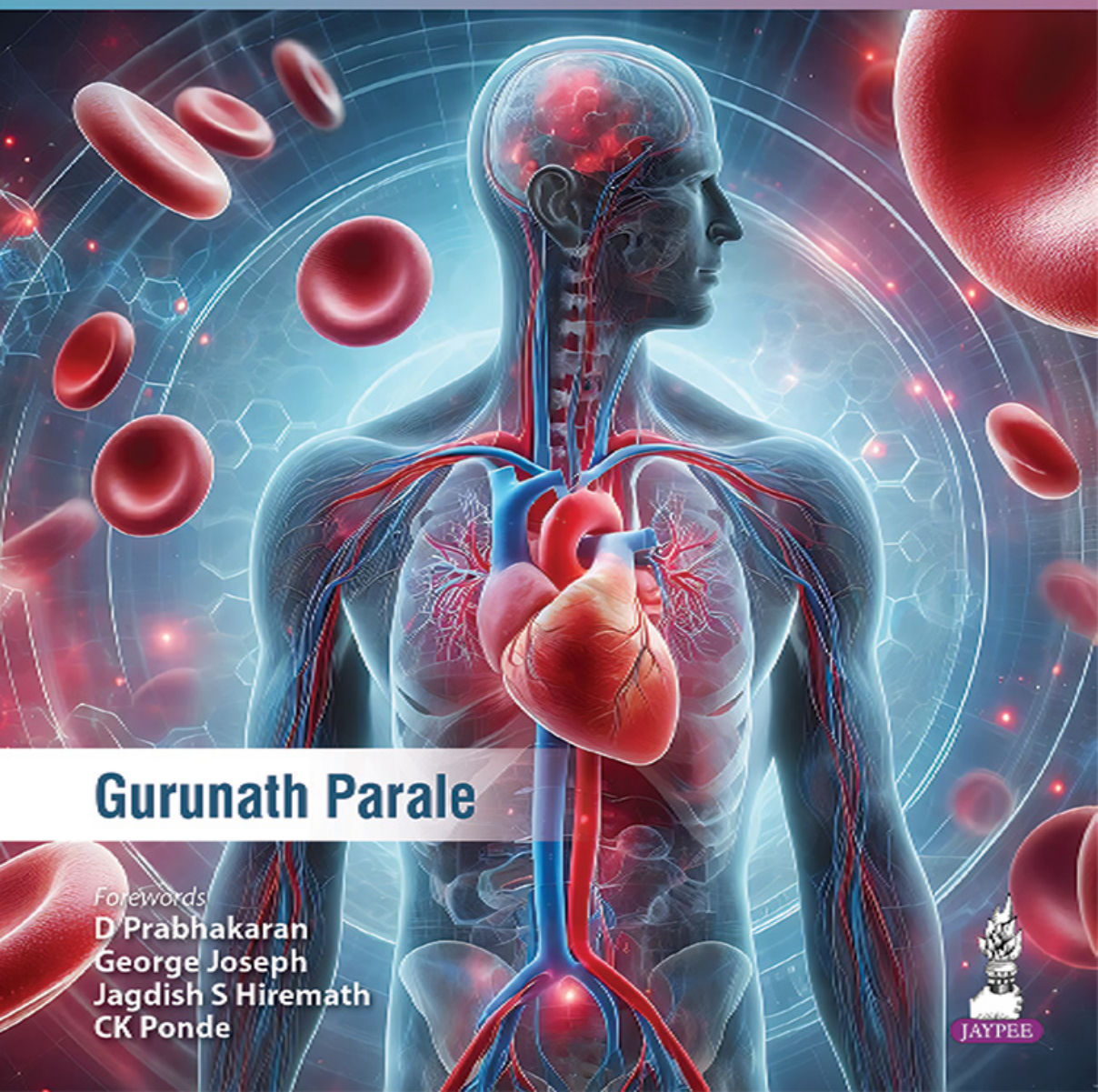
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Acute Coronary Syndrome with Comorbidities

A Therapeutic Challenge



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JAYPEE

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4

CHAPTER

Acute Coronary Syndrome Patients needing Anticoagulation

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Prologue

Two Plus Two may not be Four

A 72-year-old gentleman presented with anterior wall ST segment elevation myocardial infarction (STEMI). He was on dabigatran for atrial fibrillation (AF) with international normalized ratio (INR) of 1.6.

A 58-year-old patient who had undergone aortic valve replacement presented with acute anterior wall STEMI and heart failure. His INR was 1.9.

Main cause of worry was bleeding during primary percutaneous coronary intervention (PCI) or subsequently as triple antithrombotic therapy though ideal to prevent ischemic events but may do so at the cost of increased bleeding.

The issues before me were:

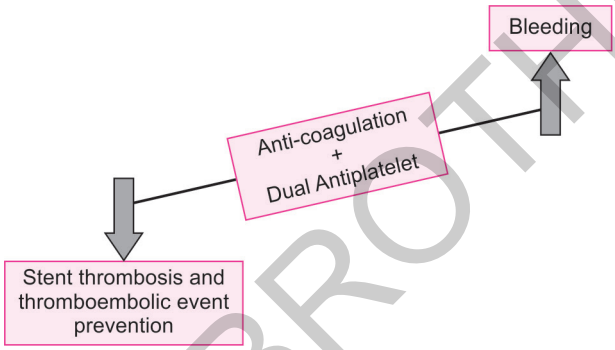
- Go ahead with primary PCI or treat conservatively
- Radial or femoral access?
- If primary PCI what should be periprocedural anticoagulation?
  - None
  - Heparin
  - Bivalirudin.
- Bare-metal stent (BMS) or drug-eluting stent (DES)
- Long-term antithrombotic regimen
  - Dual antiplatelet therapy (DAPT)
  - DAPT with vitamin K antagonists (VKAs)
  - DAPT with direct oral thrombin antagonists (DOTAs).

The author did primary PCI in both the patients with 5,000 units of IV heparin. Both patients subsequently were put on triple antithrombotic therapy.

The overall prevalence of AF is steadily increasing in the general population. Significant amount of cardiovascular mortality and morbidity is attributed to AF leading to stroke and thromboembolism.[1,2] Keeping this in mind, many of the guidelines recommend oral anticoagulants (OACs) as prophylaxis in almost all the patients with AF with a moderate to high risk of developing stroke.[3-5] As much as 5–15% of the patients with AF are known to undergo PCI sometime in their life span.[3]

Similarly, about 5–15% of the patients undergoing PCI are to known to harbor AF.[6] DAPT are invariably given to prevent stent thrombosis in almost all patients undergoing PCI and stent implantation. Therefore, a combination of antithrombotic therapy including OAC agents and antiplatelet agents is given to the patients with AF and who are subjected to PCI and stent implantation. However, some concerns are usually expressed regarding the clinical benefit of intensive combination antithrombotic therapy because of the propensity for fatal hemorrhage. The fatal bleeding event may offset the benefit of reducing the risk of ischemic damage.[7]

Park et al. in their study observed an increasing trend of AF patients undergoing PCI[1] (Flowchart 1 and Fig. 1). They also observed a rising and changing trend of anticoagulation treatment over 10 years.[1]



FLOWCHART 1: A balancing act.

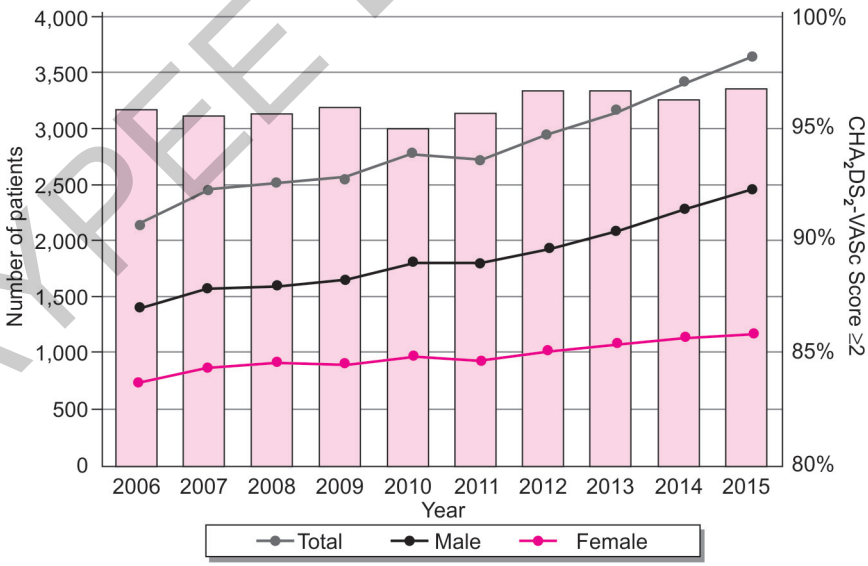


FIG. 1: The number of AF patients undergoing PCI over 10 years ($p < 0.001$).

Source: Park J, Choi EK, Han KD, et al. Temporal trends in prevalence and antithrombotic treatment among Asians with atrial fibrillation undergoing percutaneous coronary intervention: a nationwide Korean population-based study. PLoS One. 2019;14(1):e0209593.

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PRIMARY PCI VERSUS CONSERVATIVE TREATMENT

The study by Alonso et al. in subanalysis of the Global Registry of Acute Coronary Events (GRACE) describes the clinical and treatment characteristics of patients on chronic OAC presenting with STEMI.[8] They observed that the patients on OAC appeared to be less likely to undergo Cath/PCI, to receive antiplatelet and antithrombotic medications, or to receive other evidence-based therapies compared with STEMI patients not on chronic OAC. The patients on OAC carried a higher risk of adverse cardiac events. This coupled with the fact that they were less likely to receive ideal reperfusion therapy [primary PCI, coronary artery bypass grafting (CABG)] or therapy in the recommended time frame put them at additional disadvantage.

They compared users of OACs who underwent PCI to nonusers of OAC. They observed that major hemorrhagic event occurred more frequently in OAC users who underwent cath-angio or PCI. On the contrary, such hemorrhagic episodes were less frequent in the patients on conservative line and with medications. However, hospital mortality rate was higher among the patients treated conservatively (Fig. 2). As much as 20% of the medically treated patients succumbed within 6 months. This mortality

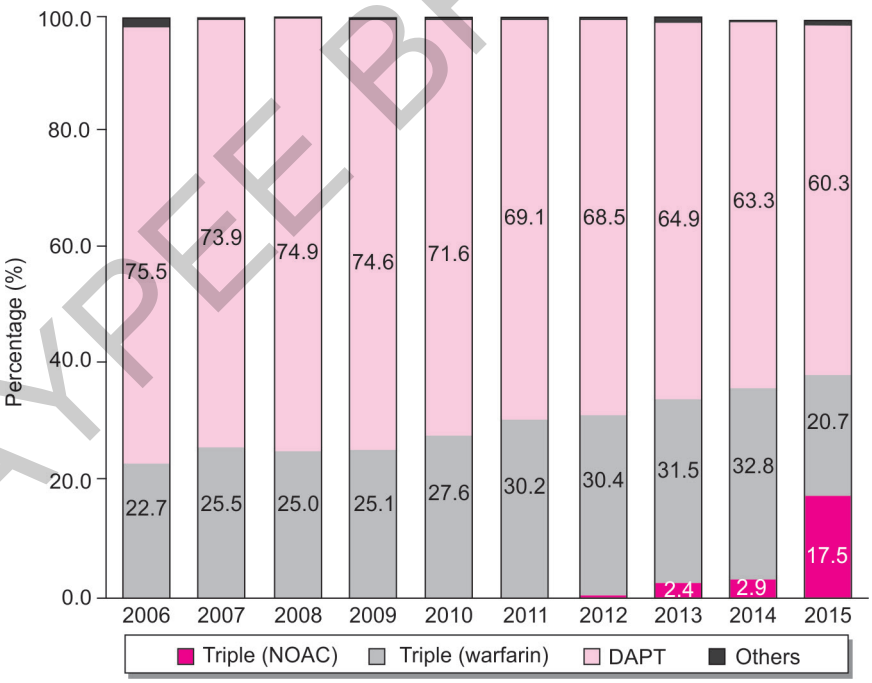


FIG. 2: The trend of anticoagulation treatment over 10 years.

Source: Park J, Choi EK, Han KD, et al. Temporal trends in prevalence and antithrombotic treatment among Asians with atrial fibrillation undergoing percutaneous coronary intervention: a nationwide Korean population-based study. PLoS One. 2019;14(1):e0209593.

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figure was just 6.9% in those patients who were subjected to PCI. Similarly, 6-month mortality was also lower when primary PCI was done. This was true irrespective of the time frame in which PCI was done.
Thus, primary PCI should be offered to patients of STEMI on OAC.

RADIAL VERSUS FEMORAL ACCESS

There is some persistent controversy regarding the preferred approach to arterial access while performing primary PCI for acute coronary syndrome (ACS). Both of these approaches were noted to be equally safe and efficacious in RIVAL study.[9] However, the radial approach was associated with some mortality benefit in a subgroup analysis of STEMI patients.[9] MATRIX trial in ACS patients too showed less major bleeding and mortality in radial versus femoral route.[10] Moreover, radial access was associated with reduced bleeding and vascular complications in many studies on patients with uninterrupted warfarin therapy undergoing PCI and who had a mean INR of 2.4.[11]

PERIPROCEDURAL ANTICOAGULATION

The most effective regimen of anticoagulation during periprocedural period for patients with ACS is not yet defined. Any such regimen must prevent ischemic complications without augmenting the risk for major bleeding episode:

- The therapeutic range of INR for patients on warfarin is 2.0–3.0. PCI is apparently safe in these patients and there is usually no need for additional periprocedural anticoagulation[12]
- At present, there are no large studies proving the safety and efficacy of performing PCI on non-VKA oral anticoagulants (NOACs) without additional anticoagulation. Until such a time, it is recommended to give additional heparin or bivalirudin and avoid glycoprotein (GP) IIb/IIIa inhibitors irrespective of the dose of NOAC. This is particularly true for those patients of STEMI where thrombogenic state is exaggerated compared to patients undergoing elective PCI[13]
- The risk of major bleeding when additional anticoagulants or antiplatelet agents are given to patients of STEMI is theoretically higher when the patients have taken a NOAC within 4 hours of presentation when compared to those who have taken the same NOAC >12 hours prior to presentation. Whenever heparin is used as the additional anticoagulant, target activated clotting time (ACT) levels (250–300 s) can be used for the purpose of titrating heparin dose. This can be done even in those patients who are on regular NOAC[13]
- *Heparin versus bivalirudin*: When compared to heparin alone or heparin combined with GP IIb/IIIa inhibitors, bivalirudin is noted to have significantly reduced risk of major bleeding as revealed in multiple trials.[14] Hence, it may be prudent to use bivalirudin instead of heparin in patients

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who have taken their last dose of NOAC within 4 hours of presentation. It is also recommended in elderly patients with impaired renal function

- *Acute antiplatelet treatment*: Compared to clopidogrel, the likelihood of major bleeding is significantly higher when ticagrelor or prasugrel is used.[15] Therefore, a loading dose of clopidogrel (600 mg) is preferable to the newer antiplatelet agents.

LONG-TERM ANTIPLATELET AND ANTICOAGULATION TREATMENT

Trials

- Dual and triple therapy with warfarin: WOEST[16]
- Dual and triple therapy with direct oral anticoagulants (DOACs): PIONEER AF-PCI,[17] RE-DUAL PCI.[18]

WOEST Trial

This is an open-label, randomized, controlled trial comparing use of clopidogrel with or without aspirin in patients taking OAC therapy and subjected to PCI. The authors of this trial concluded that compared to triple therapy with warfarin:

- Dual therapy with clopidogrel and OAC causes less bleeding
- Dual therapy with clopidogrel and OAC did not increase thrombotic events.

In their meta-analysis of DOAC trials (PIONEER AF-PCI, RE-DUAL PCI), Brunetti et al. observed that first, the use of DOACs is generally safer than and as effective as warfarin in such patients; second, dual therapy with DOACs is as safer than and as effective as triple therapy with warfarin; third, dual therapy with DOACs is as safe as and as effective as triple therapy with DOACs in patients with AF treated with PCI.[19]

Before embarking on long-term antiplatelet/anticoagulant treatment after PCI individual patient's thrombotic and bleeding risks need to be assessed.

Thrombotic Risk

Risk factors for a thrombotic (or ischemic) event (e.g. myocardial infarction, stroke that is often secondary to AF, need for repeat revascularization, or cardiovascular death) after PCI include recent ACS or stroke; complicated, multivessel coronary artery disease (CAD), particularly in patients with diabetes, a suboptimal result at the time of PCI, the need to prematurely stop antithrombotic therapy, age ≥65 years, prior stent thrombosis, and chronic kidney disease.

Bleeding Risk (Box 1)[20]

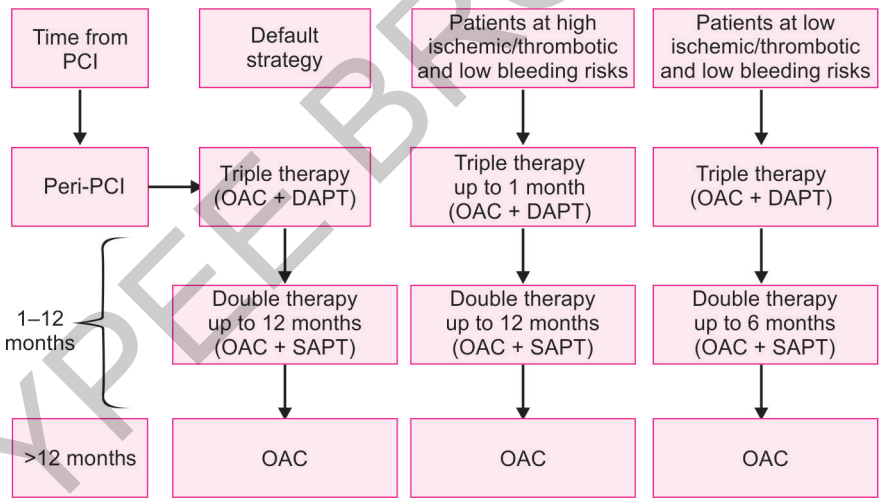
The following are recommendations for antiplatelet/anticoagulation treatment during the first 6–12 months after PCI in patients needing anticoagulation other than those with mechanical valves (Flowcharts 2 and 3):

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BOX 1 **Score to calculate bleeding risk.[20]**

- For >160 mm Hg systolic (uncontrolled hypertension) score obtained is +1
- For >2 X normal with AST/ALP/AP >3 X (abnormal liver function, cirrhosis or bilirubin) normal score obtained is +1
- For >2.26 mg/dL or 200 µmol/L (abnormal renal function dialysis, transplant, Cr) score obtained is +1
- For stroke score obtained is +1
- For bleeding (prior major bleeding or predisposition to bleeding) score obtained is +1
- For labile INR (unstable/high INR) time in therapeutic range <60% score obtained is +1
- For elderly >65 score obtained is +1
- For drugs like concomitant, antiplatelet, aspirin, clopidogrel, NSAIDs score obtained is +1
- For drugs like concomitant excess alcohol use ≥8 drink/week score obtained is +1

0–2 Low bleed risk
3–4 High bleed risk
> Very high bleed risk

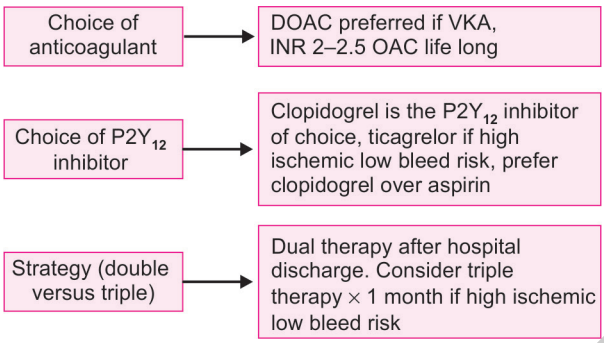


(DAPT: dual antiplatelet therapy; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; SAPT: single antiplatelet therapy)

FLOWCHART 2: 2018 AHA North American consensus white paper.

- For patients at low thrombotic and low bleeding risk, DOAC (dabigatran 150 mg twice) with *clopidogrel* plus *aspirin* (triple therapy) alternatively DOAC plus clopidogrel (dual therapy) may be chosen. If triple therapy is chosen, it is continued for 1–6 months and then aspirin is dropped. Clopidogrel 75 mg daily is continued for 6–12 months

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(DOAC: direct oral anticoagulant; INR: international normalized ratio; OAC: oral anticoagulant; VKA: vitamin K antagonist)

FLOWCHART 3: 2018 Expert Consensus.

- For patients at low thrombotic and high bleeding risk, initial treatment with DOAC (dabigatran 110 mg twice a day) plus *clopidogrel* 75 mg daily is preferred regimen for 6–12 months
- For patients at high thrombotic and low bleeding risk, the author and his colleagues suggest initial treatment with DOAC (dabigatran 150 mg twice a day) plus *clopidogrel* plus *aspirin* (triple therapy) is suggested for 1–6 months after which aspirin is discontinued and DOAC and clopidogrel continued till 12 months after PCI
- For patients at high thrombotic and bleeding risk, individualized patient decision making is essential.

After 12 months only OACs may be continued unless there is high thrombotic risk when single antiplatelet therapy (SAPT) is added.

Patients with heart valves

In patients with mechanical heart valves, non-VKA oral anticoagulants (DOACs) should not be considered alternatives to therapy with VKA and should not be used. They are contraindicated.

BARE-METAL STENT OR DRUG-ELUTING STENTS?

The ZEUS trial[21] which compared Zotarolimus DES and BMS and SENIOR trial[22] which compared any new DES with BMS and DAPT given for 1 month in both groups observed that new current generation DES are superior to BMS.

Epilogue

- Patients on anticoagulants who present with STEMI benefit from primary PCI albeit at the cost of increased bleeding
- Radial access is preferred especially if INR is more than 2.5 mainly to reduce major bleeding events

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- When patient is on VKA if INR is therapeutic (between 2 and 3), periprocedure anticoagulation may not be needed
- When patient is on DOAC, it is safer to anticoagulate notwithstanding the fact if the last dose of DOAC is within 4 hours risk of bleeding is higher
- Bivalirudin may be preferred to heparin especially in patients with increased risk of bleeding
- Current generation DES is preferred over BMS
- Vitamin K antagonists have no substitute when patient has mechanical valve
- Long-term antithrombotic treatment is determined by individual's thrombotic/bleeding risk
  - High thrombotic risk demands triple antithrombotic therapy and even up to 6 months and in low thrombotic risk patients SAPT with anticoagulation might suffice
  - In high bleeding risk patients, clopidogrel with anticoagulation may be used
- In triple antithrombotic therapy, DOAC especially dabigatran is preferred over VKA unless patient is well maintained on VKA for long time
- In triple antithrombotic or SAPT with anticoagulant therapy, clopidogrel/ticagrelor is preferred over aspirin.

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Acute Coronary Syndrome with Comorbidities: A Therapeutic Challenge

Key Features

- This book looks at some of the ignored aspects in the management of coronary artery disease associated with comorbid conditions
- Most chapters start with a prologue of real-life dilemmas that one encounters, and covers one condition per chapter
- In the middle part of the chapter, an extensive review of scarce literature available is discussed
- Most chapters conclude with an epilogue which gives some suggestions regarding management of an individual patient/comorbid condition
- The ACS with comorbid conditions discussed are the ones commonly encountered and yet pose challenge in management like ACS with stroke, with renal failure, with liver disease, with hematological disorders, etc.
- Backed by vast experience of the author, this book attempts to guide students, physicians and cardiologists to deal with complex clinical situations.

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