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From Coronaries to Cirrhosis: The Role of Percutaneous Coronary Intervention and Dual Antiplatelet Therapy in End-Stage Liver Disease

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Abstract

Drug-eluting stents (DES) have superior efficacy compared with bare metal stents (BMS) for treatment of coronary artery lesions. However, BMS continue to play an important role in percutaneous coronary intervention for patients who are at a high bleeding risk, because they require a shorter duration of dual antiplatelet therapy. However, new developments in DES and understanding of the optimal time required for dual antiplatelet therapy after percutaneous coronary intervention may further limit the use of BMS. Furthermore, the use of dual antiplatelet therapy is complicated in patients with cirrhosis, who may have coagulopathy. In this article, we present the case of a patient with cirrhosis and end-stage chronic liver disease with coronary artery disease and a proximal left anterior descending stenosis who received a DES and had multiple episodes of gastrointestinal bleeding. We review the literature addressing DES and BMS in patients at high risk of bleeding. We also review the optimal duration of dual antiplatelet therapy.

Keywords

jaundice, coagulopathy, bleeding, stent, drug eluting, vascular ectasia

Introduction

Standard balloon angioplasty for the treatment of coronary artery disease (CAD) is limited by early vessel closure and recoil. The introduction of bare metal stents led to reduced closure, but have also been limited by restenosis. A major advance in percutaneous coronary intervention (PCI) has been the introduction of drug-eluting stents because of their reduced restenosis rates. However, no matter the type of stent, dual antiplatelet therapy is essential after deployment in an effort to reduce risk of stent thrombosis.[1] Not surprisingly, bleeding risks are increased while on dual antiplatelet therapy (DAPT), especially within the gastrointestinal tract.

The recommended duration of DAPT after PCI remains an ongoing area of active controversy and investigation. Traditionally, bare metal stents (BMS) have been favored in patients who are at higher bleeding risk as they often require shorter duration of DAPT. However, there have been rapid advancements in stent technology that has shifted this paradigm. In this article, we present a case in which a patient with a high bleeding risk received a drug-eluting stent (DES) to highlight the advancements and most recent literature on DAPT after PCI.

Case Presentation

A 69-year-old man with a history of decompensated alcoholic cirrhosis complicated by esophageal varices, hepatocellular carcinoma, portal hypertensive gastropathy, CAD, chronic kidney disease, a history of gastrointestinal bleeding (GIB) due to esophageal varices, portal hypertensive gastropathy, and arteriovenous malformations presented to the emergency room with chest pain. Physical examination revealed a temperature of 36.8 °C, blood pressure 114/58 mm Hg, heart rate 87 beats per minute, respiratory rate 16 breaths per minute, and SpO_2 (oxygen saturation) of 100% on room air. He had scleral icterus, shifting dullness, and 3+ pitting edema of his lower extremities. Laboratory evaluation revealed the following: hemoglobin 8.6 g/dL, platelets 33 000/mm^3, troponin of

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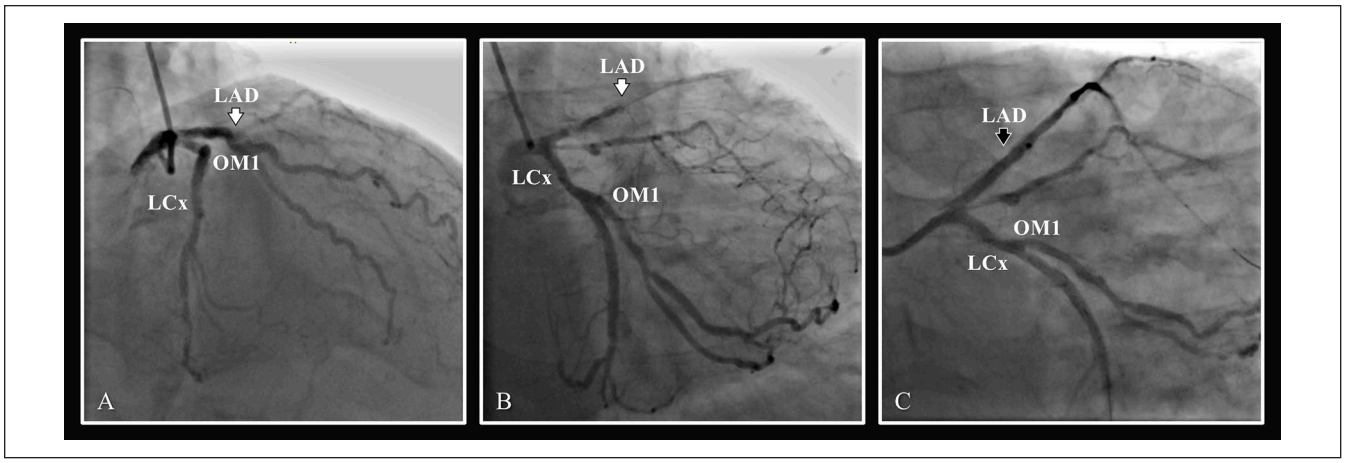

Figure 1. Coronary artery lesions. In (A) AP/caudal and (B) RAO/caudal views of proximal left anterior descending artery (LAD) with subtotal occluded lesion >95% (white arrow in each), distal vessel filling with homo and heterocollaterals. Angiography of the left circumflex (LCx) revealed mild diffuse disease, and patent first obtuse marginal (OM1) branch. In (C) is shown a LAO/caudal view of after successful percutaneous coronary infection (PCI) of proximal LAD lesion (black arrow) with TIMI III flow 2 weeks after (A) and (B) were obtained.

4.3 (ng/mL), BNP of 469 (pg/mL), creatinine 1.5 mg/dL, total bilirubin 2.8 mg/dL, international normalized ratio 1.55, and sodium 131 mEq/L with a MELD (Model of End-Stage Liver Disease) score of 23.

He underwent a left heart catheterization, which revealed >95% stenosis in the proximal left anterior descending artery (Figure 1). PCI was deferred at the time of this catheterization given his high bleeding risk. He was subsequently started on DAPT, aspirin 81 mg, and clopidogrel 75 mg daily, and was observed for 2 weeks to determine whether he would tolerate antiplatelet therapy. With no bleeding during this antiplatelet "trial," he subsequently underwent a planned PCI where a successful 3.0 × 18 mm Xience Sierra (Abbott) DES was placed (Figure 1C).

The patient was readmitted 10 days later with a chief complaint of progressive weakness and a hemoglobin of 6.8 g/dL, which was felt to represent subacute blood loss anemia. Esophagogastroduodenoscopy the next day revealed nonbleeding gastric antral vascular ectasia, mild proximal gastropathy, and multiple angioectasias in the duodenum (Figure 2) treated with argon plasma coagulation. DAPT was continued, but he required 3 units of packed red blood cells (pRBCs). After no active bleeding for 24 hours with stable hemoglobin, he was discharged home. He represented 2 weeks later with symptomatic anemia with a hemoglobin of 6.9 g/dL. He received an additional 2 units of pRBCs and a repeat esophagogastroduodenoscopy revealed continued nonbleeding angioectasias in the duodenum and stomach, which were treated with argon plasma coagulation therapy. The cardiology service was consulted and recommended continuing DAPT for 3 months. He received intravenous iron and was started on octreotide for arteriovenous malformation bleeding and discharged home. He was readmitted 2 days later with weakness, dehydration, and acute kidney injury (AKI); his bilirubin had climbed to 3.5 mg/dL, and his MELD score to 30. During this admission he developed melena and hypotension, and he was transferred to the intensive care unit, where he required 2 units of pRBCs and 1 unit of platelets. His aspirin was discontinued and he was continued on clopidogrel. Although he was stabilized and transferred back to the floor, he developed oliguria and progressive renal failure, felt to be from the hepatorenal syndrome, and he was discharged home with hospice.

Discussion

The patient ultimately died due to decompensation of his liver disease and AKI, believed to be hepatorenal syndrome. His course was clearly complicated by his cardiac condition, and secondary GIB. Given this scenario, it could be argued that the patient would have been better served with a BMS instead of a DES. BMS have been favored over DES and DAPT for patients at high risk of bleeding.

The duration of DAPT in the 2016 American College of Cardiology/American Heart Association updated guidelines on DAPT is predicated on whether the CAD is stable or unstable.[2] In patients with stable CAD, current guidelines recommend that patients receiving a DES should be on DAPT therapy for at least 6 months. If receiving a BMS, at least 1 month of DAPT is recommended.

After stent deployment, DAPT is necessary as an intraluminal stent serves as a foreign body and is prothrombotic. There is a clear benefit to DAPT versus aspirin therapy alone after PCI.[3] Antiplatelet therapy minimizes thrombus formation as endothelialization takes place over the stent. In general, BMS and DES stents have a similar metallic

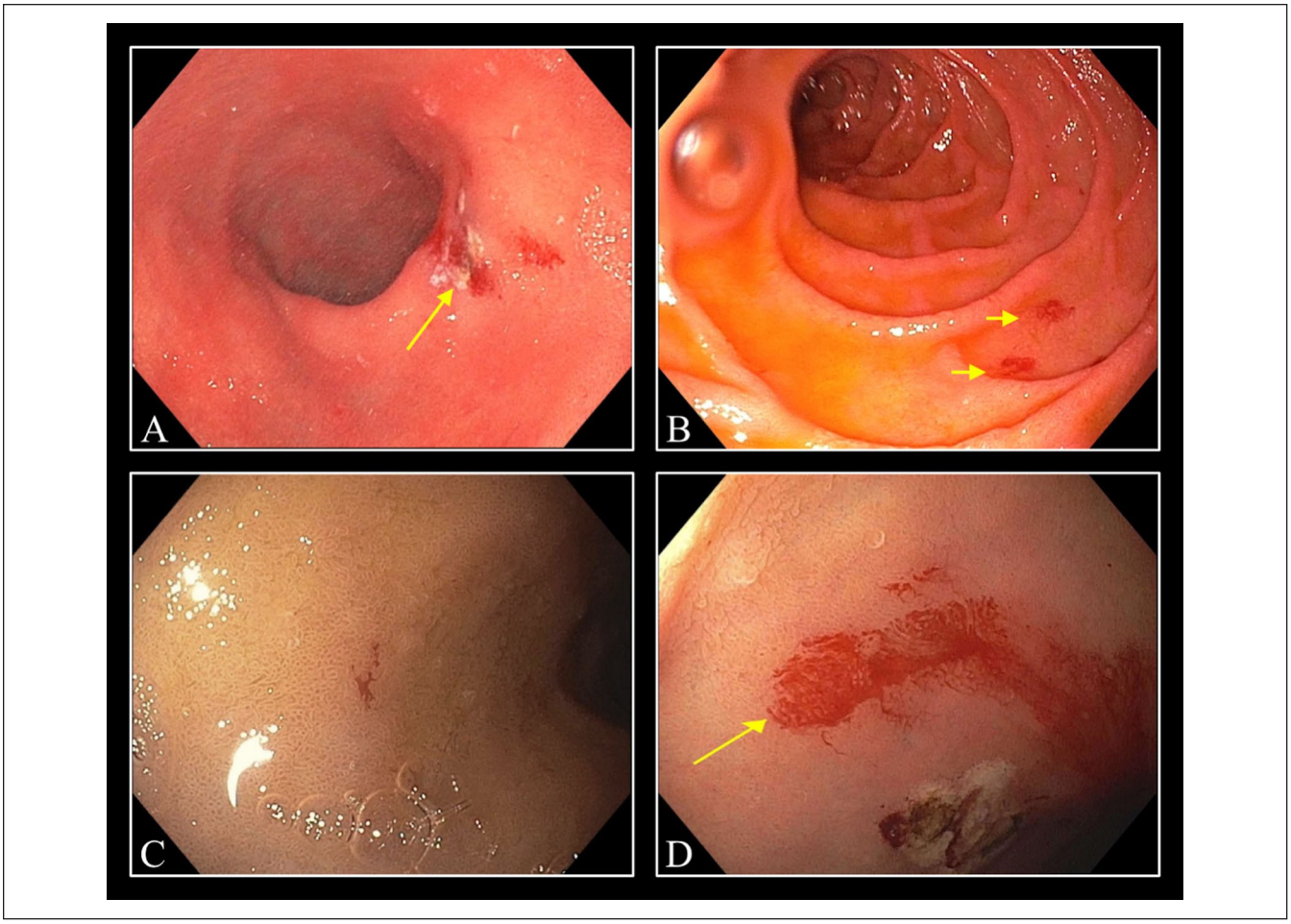

Figure 2. Endoscopic bleeding lesions. On initial esophagoastroduodenoscopy 10 days after percutaneous coronary infection (PCI), vascular ectasias were identified in the duodenal bulb (A) and second portion of the duodenum (B). Yellow arrows point to ectasias. At the time of repeat esophagoastroduodenoscopy 2 weeks after initial endoscopy, evidence of mild portal hypertensive gastropathy was identified, along with a small non bleeding duodenal bulb vascular ectasia (center of the image; C) and a bleeding duodenal bulb vascular ectasia (D). The yellow arrow points to the edge of the bleeding lesion.

backbone. After endothelialization occurs over the stent, the stent's surface is no longer exposed to the vessel. Thus, the risk of thrombosis is not as high and the DAPT benefits are diminished. With BMS, this endothelialization occurs approximately within a month; thus, the current guidelines recommend 1 month DAPT after deployment. However, after endothelialization of the BMS, the risk of stent restenosis remains.

Drug-eluting stents are coated with polymers that elute an antiproliferative medication that prohibits neointama growth, the main mechanism of restenosis. Restenosis and need for repeat target vessel revascularization typically occurs within the first year of deployment. It is within this 1 year period where DES have shown their superiority to BMS. However, first-generation DES have been associated with higher rates of late (>1 year) stent thrombosis. But with advancements in stent design, second-generation DES have improved late thrombosis rates. New DES are made with thinner struts allowing for less turbulent flow and coated with less toxic antiproliferative drugs. These are considered superior to BMS in safety, reduce myocardial infraction and stent thrombosis, but also efficacy with reduction in target vessel revascularization.[4] The only advantage with BMS is the shorter duration of required DAPT, an attractive option for patients who are at high bleeding risk. However, rapid advancements in DES technology and the latest literature suggest that the perceived benefits of BMS are likely diminishing.

PCI in Cirrhosis

The patient presented here clearly had an elevated bleeding risk, based on the previous history of GIB—and also suggested by his known portal hypertension. Although abnormalities in the production of coagulation factors by the liver are well established, the effect on bleeding remains highly controversial.[5,6] Additionally, this patient also had

Table 1. Studies Examining Shortened DAPT Therapy.

Study	Stent type	Results	Stent availability in the United States?	Included liver disease?
LEADERS FREE (2015)[17]	Polymer-free umirolimus-coated stent (BioFreedom) versus BMS (Gazelle)	1-month DAPT with umirolimus-coated stent superior to BMS in safety and efficacy	No	Inclusion criteria, 21 of 2432 (0.0086%)
ZEUS (2015)[18]	Zotarolimus-eluting (Endeavor Sprint Stent) versus 5 different BMS	Lower 1-year MACE in DES versus BMS after median 32 days DAPT	No longer commercially available	No mention[a]
SENIOR (2018)[19]	Bioabsorbable polymer DES (Synergy) versus thin strut BMS (Omega or Rebel)	1-Month DAPT with DES superior in all-cause mortality, MI, stroke, TVR, to BMS in patients age >75 years	Yes	No mention
TWILIGHT (2019)[20]	Unspecified DES	In high bleeding risk patients, 3-month DAPT followed by ticagrelor monotherapy for 12 months results in less bleeding compared with 12 months DAPT without increased risk of death, MI, and CVA		Exclusion criteria
STOP-DAPT2 (2019)[21]	Cobalt chromium everolimus-eluting stent (Xience series, Abbott Vascular)	1-Month DAPT followed by clopidogrel monotherapy versus 12-month DAPT with reduction in bleeding and CV events	Yes (our patient received)	10 of 3009 (0.3%)
LEADERS FREE II (Ongoing)	Polymer-free biolimus A9 drug-coated stent (BioFreedom)	Trial designed to gain device registration with the FDA	TBD	Inclusion criteria
MASTER DAPT (Ongoing)	Ultimaster or Ultimaster TANSEI siroliumus-eluting stent (Terumo)	1-Month DAPT followed by single antiplatelet (aspirin vs clopidogrel at physician discretion) versus standard DAPT for at least 6 months followed by single antiplatelet therapy	No	No mention[a]

Abbreviations: DAPT, dual antiplatelet therapy; BMS, bare metal stent; MACE, major adverse cardiovascular event; DES, drug-eluting stent; MI, myocardial infarction; TVR, target vessel revascularization; CVA, cerebrovascular accident; CV, cardiovascular; FDA, Food and Drug and Administration.
[a]No explicit mention of cirrhosis or end-stage liver disease; however, inclusion criteria included "Systemic conditions associated with an increased bleeding risk (eg, hematological disorders), including a history of or current thrombocytopenia defined as a platelet count $<100\,000/mm^3$ ($<100 \times 10^9/L$), or any known coagulation disorder associated with increased bleeding risk."

hypersplenism and a markedly reduced platelet level, likely also contributing to an elevated bleeding risk. The DAPT "trial," or pretreatment prior PCI is established and reduces MACE (Major Adverse Cardiovascular Events).[7] Anecdotally, these trials have unmasked occult bleeds.[8]

Patients with cirrhosis and CAD who undergo PCI compared with medical management have increased adverse events, AKI, and major bleeding, without increased mortality.[9] The risk of adverse events increased with severity of liver disease based off Child-Pugh classification suggesting medical management may be more appropriate for Child-Pugh class C patients.

Yet retrospective studies, mainly from literature related to evaluation for liver transplantation in patients with simultaneous CAD, indicate that PCI is safe and feasible in end-stage liver disease.[10,11] However, evidence on the use of DES is limited. In a study using the Nationwide Inpatient Sample (from 2005 to 2012) that examined 1 051 242 PCIs, 12 342 were performed in patients with cirrhosis[12]; BMS and DES were 45% and 55%, respectively. In this study, postprocedure overall complication rates were 7.1%, whereas the overall postprocedural in hospital mortality rate over these years was 3.63% in patients who received PCI in the setting of cirrhosis. There was a statistically significant mortality difference between DES versus BMS (2.35% vs 5.18%, $p < 0.001$), hemorrhagic or acute blood loss anemia requiring transfusion (1.69% vs 3.36%, $p = 0.008$). However, baseline characteristics between patients who received BMS versus DES were significantly different. Patients receiving BMS tended to be placed in more emergent situations, such as STEMI (ST-elevation myocardial infarction), cardiogenic shock, or required intraaortic balloon pump. Additionally, BMS were more likely to be used in patients with a history of anemia, coagulopathy, and malignancy—supporting their use in patients with higher bleeding risks.

In a case-control study that examined DAPT in cirrhotic patients in the setting of CAD after PCI determined that GIB was significantly increased (22.1% vs 5%) at 1 year in

patients receiving DAPT, but all-cause mortality was similar (20.6% vs 21.6%).[13] Interestingly, this same study found that there was no significant difference between GIB in patients who received BMS versus DES. Of note, multivariate analysis revealed that the use of proton pump inhibitors was highly protective against GIB. It should be noted that there are no data directly regarding BMS versus DES in patients with CAD undergoing PCI who are listed for transplant. Anecdotally, DES are favored, but if a surgery is to be expected shortly after PCI, a BMS is often considered.

DAPT Duration in Cirrhosis

Within the last 5 years, there have been a proliferation of trials examining the optimal duration for DAPT. Although some experts have recommended extending the duration of DAPT, which is currently being investigated,[14] other trials have examined shortening the duration of the DAPT (Table 1). There appear to be more favorable outcomes in DES with shortened DAPT duration, but caution is required in interpreting these results because many of these stents are not available in the United States. Even more important, the current literature and its applicability to our patient and others with end-stage liver disease remains unclear. Very few trials included patients with chronic liver disease and in some studies, these patients were excluded.

Recently, a 13-year retrospective cohort study using Taiwanese Nationwide Insurance Research Database evaluating patients with myocardial infarction and known cirrhosis compared outcomes with propensity-matched noncirrhotic patients with at least 3-month DAPT.[15] In the 1-year follow-up period, cirrhotic patients had significantly increased mortality rates (32.7% vs 23.7%, hazards ratio [HR] = 1.49) and GIB (28.0% vs 20.2%, subdistribution HR = 1.23), but a decreased risk of recurrent MI (6.0% vs 8.7%, subdistribution HR = 0.71). DAPT compared with single antiplatelet therapy (aspirin or clopidogrel alone) was associated with decreased all-cause mortality with similar bleeding risk.

Minimal data exist with regard to the severity and type of GIB on DAPT after PCI. In the previously cited case-control study, despite having increased total GIB bleeding on DAPT, no increased variceal bleeding was observed.[15] Although this may be limited by the small sample size. However, there are data that suggest cirrhotics who have been anticoagulated are at increased variceal hemorrhage, with recommendations for aggressive variceal management prior to initiation of anticoagulation.[16] There are no such recommendations prior to DAPT initiation.

Conclusions

In summary, the use and optimal duration for DAPT after PCI in patients with cirrhosis remains an ongoing area requiring further research. As highlighted in our patient, DAPT is likely to increase the risk of bleeding in patients with cirrhosis and portal hypertension. Furthermore, data on the use of PCI comparing BMS versus DES in cirrhosis is required. With the advances in DES technology and many trials suggesting that a shortened course of DAPT is both safe and effective, the question as to whether this can be translated to the cirrhotic population remains. These challenges and questions should frame future investigation.

Author Contributions

Taylor C. Remillard: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.
Don C. Rockey: Study concept and design; interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; supervisory activities.
All authors have approved the final version of the manuscript.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Informed consent for patient information to be published in this article was not obtained because this is not required by our institution.

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patients with non–ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation* 2016;134:e123-e155. doi:10.1161/CIR.0000000000000404

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