



Review

Prevention and management of gastroesophageal varices

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Bleeding from gastroesophageal varices is a serious complication in patients with liver cirrhosis and portal hypertension. Although there has been significant improvement in the prognosis of variceal bleeding with advancement in diagnostic and therapeutic modalities for its management, mortality rate still remains high. Therefore, appropriate prevention and rapid, effective management of bleeding from gastroesophageal varices is very important. Recently, various studies about management of gastroesophageal varices, including prevention of development and aggravation of varices, prevention of first variceal bleeding, management of acute variceal bleeding, and prevention of variceal rebleeding, have been published. The present article reviews published articles and practice guidelines to present the most optimal management of patients with gastroesophageal varices. (**Clin Mol Hepatol 2018;24:20-42**)

Keywords: Cirrhosis; Portal hypertension; Ligation; Obturation; Obliteration

INTRODUCTION

Gastroesophageal varices (GEVs) are frequent complication of liver cirrhosis and a leading cause of mortality in patients with liver cirrhosis. Portal hypertension, which is the most common complication of liver cirrhosis, is the main determinant for development of GEVs. Increased intrahepatic vascular resistance to portal flow leads to the development of portal hypertension, which is aggravated by splanchnic vasodilatation and increase in portal blood flow by hyperdynamic circulation.¹⁻³ When the portal pressure increases above a threshold, collaterals develop at the site of communication between the portal and systemic circulation.⁴ In this condition, GEVs are the most important collaterals, and with the aggravation of portal hypertension, they grow and eventually rupture.⁵ Bleeding from GEVs is a major complication of portal hy-

perfusion and a leading cause of mortality in patients with liver cirrhosis.^{6,7} Therefore, prevention of variceal development and progression, prevention of bleeding from GEV, appropriate management for acute bleeding from GEV, and prevention of variceal rebleeding are critical in patients with liver cirrhosis. Recently, a number of studies regarding these topics have been published. Therefore, we will review the published results and discuss about appropriate management for these patients.

NATURAL HISTORY

In a previous study, GEVs were present in 52.2% of patients who performed endoscopy for variceal screening.⁸ The incidence of GEVs was significantly higher in patients with Child-Pugh class

Abbreviations:

BRTO, balloon-occluded retrograde transvenous obliteration; CI, confidence interval; CSPH, clinically significant portal hypertension; EBL, endoscopic band ligation; EIS, endoscopic injection sclerotherapy; EVO, endoscopic variceal obturation; EVs, esophageal varices; GEV, gastroesophageal varices; GOV, gastrooesophageal varices; GVs, gastric varices; HVP, hepatic venous pressure gradient; IG, isolated gastric varices; ISMN, isosorbide mononitrate; NO, nitric oxide; NSBBs, nonselective beta-blockers; PARTO, plug-assisted retrograde transvenous obliteration; PRBC, packed red blood cell; PTFE, polytetrafluoroethylene; RCT, randomized controlled trial; RR, relative risk; TIPS, transjugular intrahepatic portosystemic shunt

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B/C than those with Child-Pugh class A (71.9% vs. 42.7%, $P=0.02$).⁹ In another study, varices were present in 37.9% of patients with liver cirrhosis: 34.7% in patients with compensated cirrhosis and 47.9% in those with decompensated cirrhosis.⁸

The incidences of esophageal varices (EVs) in cirrhotic patients without varices at baseline are 5-9% at 1 year, 14-17% at 2 years, and 21-28% at 3 years.^{4,10} In another study, cumulative incidence of variceal development over 10 years was 44% in patients with cirrhosis but without varices at baseline.⁸ The main risk factor of variceal development in these patients is a hepatic venous pressure gradient (HVPG) >10 mmHg.⁴ Small EVs usually progress to large varices and incidence of progression from small to large EVs is 12% at 1 year, 25% at 2 years, and 31% at 3 years.¹⁰ The independent risk factors of progression of EVs are alcoholic cirrhosis, decompensated disease (Child-Pugh class B/C), the presence of red color sign at first endoscopy, and splenomegaly.¹⁰

The 1-year incidence of variceal bleeding in patients with cirrhosis and varices without previous history of bleeding is approximately 12% (5% for small varices and 15% for large varices) and main risk factors of bleeding are larger varices, presence of red color signs over the varices, and decompensated disease (Child-Pugh class B/C).¹¹ In a previous study for the evaluation of the natural history of small EVs, the 2-year EV bleeding rate was 12% and the presence of red color sign was the only independent risk factor.¹⁰ Although the mortality rate has been decreased significantly during recent several decades with improvement in diagnostic and therapeutic modalities for its management,^{12,13} mortality rate still remains high as 12-22%.¹⁴⁻¹⁶

In addition, rebleeding is very frequent as 60% within 1 year without appropriate treatment for the prevention of rebleeding.¹⁷ A previous study suggested that HVPG is significantly associated with the risk of rebleeding and patients with HVPG >20 mmHg within 24 hours of variceal bleeding have higher risk of recurrent bleeding within 1 week and higher risk of failure in bleeding control.^{18,19}

THERAPEUTIC OPTIONS

Pharmacological treatment

Because the splanchnic vasodilatation is the main step in the development and progression of portal hypertension, drugs which can lead splanchnic vasoconstriction, such as nonselective beta-blockers (NSBBs), terlipressin, somatostatin, and its analogues

(octreotide, vapreotide) reduce portal pressure and, currently, these drugs are widely used in the management of GEVs. NSBBs, such as propranolol and nadolol, reduce portal blood flow through β_1 -blockade (reduction of cardiac output) and β_2 -blockade (splanchnic vasoconstriction).²⁰ Various studies suggested that NSBBs is effective in the prevention of bleeding from EVs and recent practice guidelines recommend use of NSBBs for reducing portal pressure, leading to primary and secondary prophylaxis against variceal bleeding in patients with cirrhosis and high-risk EVs.²¹

Carvedilol is an NSBB, but it has also anti- α_1 -adrenergic (vasodilator) activity. Therefore, it can reduce portal pressure not only by splanchnic vasoconstriction, similar with other NSBBs, but also by intrahepatic vasodilation and reduction of intrahepatic pressure. HVPG reduction by carvedilol is significantly greater than by other NSBBs, propranolol or nadolol, in a systemic review.²² However, it also induce more significant decreases in arterial pressure. The optimal dose is 12.5 mg once a day because higher doses have no additional benefit in HVPG with higher reduction of arterial pressure.^{23,24} Although several studies evaluated the efficacy of carvedilol in the primary and secondary prophylaxis against variceal bleeding, results are conflicting.

Recent studies suggested that simvastatin enhances endothelial nitric oxide (NO) synthase activity and up-regulates NO production, which in turn, leads intrahepatic vasodilatation and decrease in portal pressure.^{25,26} However, the effect on the GEVs of simvastatin is unclear.

Endoscopic treatment

Endoscopic injection sclerotherapy (EIS) is a procedure injecting sclerosant such as ethanolamine oleate, tetradecyl sulphate, or absolute alcohol directly into varices or surrounding areas of varices. Injected sclerosant induces endothelial damage and thrombosis of varices resulting in sclerosis and resolution of varices. EIS have been applied to the management of esophageal variceal bleeding since the mid-1970s.²⁷ However, EIS has some complications such as pulmonary edema, renal failure, esophageal ulceration, stricture, perforation, and variceal rebleeding.^{28,29} As endoscopic band ligation (EBL) showed improved survival, decreased risk of rebleeding, and less adverse effects,^{30,31} EBL has replaced EIS as the first-line treatment in the manage of esophageal variceal bleeding.³¹⁻³⁴

Nowadays, EBL is considered as the endoscopic treatment of choice for the hemostasis and prophylaxis of bleeding from EVs

because of the superior effectiveness and safety compared to EIS.³⁵⁻³⁷ In addition, EBL require fewer treatment sessions to achieve variceal obliteration, lower rebleeding rates, and fewer complications compared to EIS.³⁷ In EBL procedure, rubber band captures all or part of varices, followed by occlusion from thrombosis. Then, variceal tissue necrosis, leaving a superficial mucosal ulceration. As EBL does not use sclerosant, it rarely damages deep esophageal wall. Also, EBL promotes the development gastric collaterals, because collateral vessels near the cardia decreases after EBL.^{38,39} EBL should be repeated every 2-4 weeks until variceal eradication is achieved, which is usually defined as the disappearance of varices or decrease in size to grade 1 and too small for EBL without red color sign. Because of high recurrence rate of varices after eradication by EBL, indefinite endoscopic monitoring to detect recurrence of high-risk varices is recommended. High recurrence rate after eradication by EBL could be explained of its nature, only act by mechanical strangulation without any effect on portal hypertension. However, recurrence rate after EBL is significantly higher than after EIS, although both procedures are local therapies.^{40,41} It is probably because the two procedures differ in their mechanism of action. In EBL, the effect of EBL effect is usually limited to the mucosa and submucosa, while perforating veins between the paraesophageal veins and submucosal veins are preserved. In contrast, EIS eradicates EVs through a chemical reaction that leads to fibrosis; the effects of EIS extend into the deeper layers, obliterating the perforating veins. EV recurrence is associated with an increased risk of bleeding, and it is therefore crucial that patients be monitored closely after treatment for EVs.

Endoscopic variceal obturation (EVO) has been reported to be effective in the treatment of acute bleeding from gastric varices (GVs) and prevention of GV rebleeding.⁴²⁻⁴⁵ Cyanoacrylate is a monomer that rapidly undergoes polymerization when it contacts with the hydroxyl ions which present in water. The double bonds present in the monomer become single bonds, causing them to link together in enormous chains, changing from liquid to a hard acrylic plastic material. Cyanoacrylate is usually mixed with lipiodol in 1:1 ratio. Cyanoacrylate glue is injected directly into the gastric varix,⁴⁶ then polymerizes rapidly and plugs the lumen of varices, resulting in hemostasis of variceal bleeding. The needle should be withdrawn immediately after the injection to prevent its impaction into the tissue. Injection could be repeated until the varix is hard to palpation with a catheter or biopsy forceps. Glue cast is usually extruded into the stomach within 1-3 months after injection.⁴⁷ Adhesive agent gradually induces inflammatory response and elimination of vascular endothelial cells, leading to

resolution of varices. EVO is associated with complications such as infection, fever, perforation, gastric ulcer, damage to the endoscope, and peritonitis. Moreover, it has a risk of embolization, especially when insufficient amount of cyanoacrylate was injected in varices, followed by leakage into collateral vessels to other major organs.⁴⁸⁻⁵²

Radiologic treatment

Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure that establish a direct pathway between the hepatic vein and the portal vein by inserting stent to decompress the portal hypertension. By lowering portal pressure, TIPS manages variceal bleeding via reducing variceal blood flow, and also controls other complications caused by portal hypertension. The efficacy of TIPS in the treatment of gastric variceal bleeding refractory to endoscopic therapy and prophylaxis for variceal rebleeding has been reported in a recent meta-analysis.⁵³ Success rate, procedure-related mortality, 30-day mortality of TIPS procedure, ranged from 93-100%, 0-2%, 3-15%, respectively.⁵⁴⁻⁶⁰ The major disadvantage after TIPS procedure is variceal rebleeding caused by obliteration or stenosis of shunt. To prevent rebleeding of varices, hepatic venous pressure gradient should be controlled lower than 12 mmHg,⁶¹ and routine surveillance tests using ultrasound with doppler should be done even in asymptomatic patients.⁶² The TIPS may lead to other adverse events. Technical complications at procedure including transcapsular puncture and extrahepatic portal vein puncture were reported.⁶² Deterioration of hepatic function and development or aggravation of hepatic encephalopathy (25-30%) may occur after TIPS.⁵⁴ Most cases are relieved by medical therapy, however, encephalopathy is refractory to conservative treatment in 3-7%, decreasing diameter of shunt by inserting coil or vascular plug into stent, or stent graft might be needed.⁶³ In addition, as central venous pressure is elevated by increased systemic blood flow through porto-systemic shunt, patients with right sided heart failure, severe pulmonary hypertension, and severe tricuspid regurgitation are contraindicated to TIPS. Primary prevention of variceal bleeding, unrelieved biliary obstruction are also absolute contraindications of TIPS.⁶² In last decades, polytetrafluoroethylene (PTFE)-covered stents have been introduced, resulting in marked improvement of long-term shunt patency compared to bare metal stent. Recent studies have reported higher rate of patency and lower rate of hepatic encephalopathy with PTFE-covered stent.^{64,65}

Balloon-occluded retrograde transvenous obliteration (BRTO) is

an interventional radiologic technique used for bleeding gastric varices and ectopic varices.⁶⁶ BRTO procedure is to induce thrombotic obliteration of gastric varices by injecting an endovascular sclerosant such as ethanolamine oleate in to the gastric varices through the gastrosplenic or gastrocaval shunt while variceal blood flow is stopped by retrograde balloon occlusion.⁶⁷⁻⁷⁰ Gastric varices frequently have a spontaneous gastrosplenic shunt account as a main draining vein, however, approximately 15% of patients with GVs have other various portosystemic venous pathways, such as the left inferior phrenic, pericardiac, and azygous-hemiazygous veins and BRTO is not available in these patients.⁷¹⁻⁷⁴ BRTO has an important advantage over other treatments. As BRTO has potential of increasing portal blood flow, it can be performed in patients with impaired hepatic function and hepatic encephalopathy.^{68,71,75} However, increased portal venous pressure after BRTO would induce aggravation of esophageal varices and increased ascites. The risk for worsening of esophageal varices after BRTO was reported to be 24.9-58% at 3 years.^{72,76,77} Therefore, follow-up endoscopy is required following BRTO. Adverse events, such as abdominal pain, back pain, and low grade fever, are often observed during or after BRTO.⁷⁸ Also, BRTO has several complications related to EO such as hemolysis, hemoglobinuria, pulmonary edema, disseminated intravascular coagulation, anaphylactic reaction, and even severe renal dysfunction.^{69,79} Reported success rates of BRTO has been 87-100%, the relapse rate of varices is 0-10%.^{68,70-72,75,76,80}

Recently, plug-assisted retrograde transvenous obliteration (PARTO) was proposed as modified BRTO to minimize complications of BRTO, associated with the use of sclerosant and balloon indwelling.^{68,81-89} In PARTO, balloon occlusion catheter and sclerosant are replaced with a vascular plug/coils and gelatin sponge.⁹⁰⁻⁹² Recent studies reported 100% of technical success rate and 98.6% of clinical success rate of PARTO in thrombosis of the gastrosplenic shunt and GVs.^{90,93} Procedure-related complications, rebleeding of GVs or hepatic encephalopathy was not found in observation period. PARTO has several advantages. First, PARTO prevents procedure-related complications and decreases the procedure time, because vascular plug and gelatin sponge can promote rapid and complete embolizations without complications.^{91,94} Second, as PARTO does not use sclerosants, it does not require selective embolization of efferent veins in most cases. However, PARTO also has potential worsening of EVs and ascites like BRTO. EVs were newly developed in 10% of patients who did not have EVs before PARTO, and progressed in 16.7% of patients who had EVs before PARTO. Ascites was newly appeared in 15%

of patients who did not have ascites before PARTO, and progressed to larger amount in 8.3% of patients who had ascites before PARTO.

PREVENTION OF VARICEAL DEVELOPMENT AND PROGRESSION

Because development of GEVs is a direct consequence of portal hypertension, reduction of portal pressure by NSBBs from the early stage of liver cirrhosis might ameliorate the development of GEVs. Similarly, several animal studies suggested that early administration of NSBBs reduced the development of porto-systemic shunting.^{95,96}

A previous placebo-controlled study evaluated whether NSBBs could prevent the development of varices in 213 patients with cirrhosis and portal hypertension without GEVs.⁴ Patients were randomized to receive timolol (n=108) or placebo (n=105) and the mean follow-up duration was 54.9 months. The rate of primary end-point, the development of varices or bleeding from varices, did not differ between two groups (39% vs. 40%, $P=0.89$), while the incidence of serious adverse events was significantly higher in the timolol group than the placebo group (18% vs. 6%, $P=0.006$).⁴ Therefore, current practice guidelines do not recommend the use of NSBBs for the prevention of the development of varices.²¹

Several studies evaluated whether NSBBs could prevent or delay the growth of small varices, but the results are controversial. One study showed a significant reduction of the progression to large EVs in the nadolol group compared to the placebo group in patients with cirrhosis and small EVs (7% vs. 31% at 2 years, 20% vs. 51% at 5 years; $P<0.001$),⁹⁷ while another study showed no benefit of propranolol for the prevention of progression to large varices (23% in the propranolol group vs. 19% in the placebo group, $P=0.786$) although reduction of portal pressure was significantly greater in the propranolol group.⁹⁸ A recent meta-analysis suggested that NSBBs are not effective in preventing the progression of small to large varices.⁹⁹ Therefore, further studies are required to confirm to start NSBBs at this stage. A recent study showed that the incidence of progression to large varices was significantly lower in the carvedilol group than the placebo group during 24 months (20.6% vs. 38.6%, $P=0.04$) and they suggested that carvedilol is safe and effective in delaying the progression of small to large EVs in patients with cirrhosis.¹⁰⁰

The main treatment target of the action of NSBBs is a splanchnic vasoconstriction to ameliorate the hyperdynamic circulation

and reduce portal pressure. Therefore, NSBBs might be more effective in patients with moderate or severe splanchnic vasodilatation with clinically significant portal hypertension (CSPH; defined as ≥ 10 mmHg of HVPG) and hyperdynamic circulation, while those might be ineffective in patients with an early-stage cirrhosis when splanchnic vasodilatation is not developed yet or its severity is very mild. In a previous study of patients with 273 patients with cirrhosis without any previous decompensation, without EVs or with small varices without red signs, the response to NSBBs was significantly greater in patients with CSPH than those with sub-clinical portal hypertension (HVPG >5 and <10 mmHg).¹⁰¹ Therefore, negative results of NSBBs in the previously mentioned studies might be due to the inclusion of patients with an early-stage liver cirrhosis. While, carvedilol reduce portal pressure by the anti- α_1 -mediated decrease in intrahepatic resistance as well as splanchnic vasoconstriction.¹⁰² Because the intrahepatic vasoconstriction is the main pathologic mechanism of the development of portal hypertension in the early-stage liver cirrhosis, it could be more effective in the prevention of progression of varices in patients with an early-stage cirrhosis.

MANAGEMENT OF ESOPHAGEAL VARICES

Primary prophylaxis

Because of the poor prognosis in patients with variceal bleeding, current guidelines recommend primary prophylaxis against VB in patients with high risk of bleeding. Patients with high risk of bleeding consist of patients with medium/large varices, those with small varices with red color signs, and those with decompensated liver disease and small varices.¹¹

Recommended modalities for primary prophylaxis against VB are NSBBs or EBL. In times past, isosorbide mononitrate (ISMN) was considered as a potential drug for primary prophylaxis, because of its ability of significant reduction of portal pressure.¹⁰³ However, in a subsequent trial comparing ISMN with propranolol, although incidence of VB did not differ between two groups, mortality rate was significantly higher in the ISMN group (72% vs. 48%, $P=0.006$).¹⁰⁴ Therefore, ISMN is not recommended as monotherapy in primary prophylaxis. Various studies and meta-analyses confirmed that NSBBs is superior to no therapy or placebo in preventing first VB.^{99,105-108} However, the effect on mortality of NSBBs in this setting is controversial.^{99,105-108} In a previous meta-analysis, EBL reduce the risk of first VB (relative risk [RR], 0.36;

95% confidence interval [CI], 0.26-0.50) and mortality (RR, 0.55; 95% CI, 0.43-0.71) compared to no treatment.¹⁰⁹ While, in this meta-analysis, although EBL reduce the risk of first VB (RR, 0.48; 95% CI, 0.24-0.96), there was no difference in mortality (RR, 0.95; 95% CI, 0.56-1.62) when compared with NSBBs.¹⁰⁹ Similarly, the efficacy of EBL for the prevention of first variceal bleeding was similar with or superior to NSBBs without any differences in mortality in other meta-analyses.¹¹⁰⁻¹¹³

Therefore, current practice guidelines recommend that either NSBBs or EBL for the prevention of the first variceal bleeding in patients with medium or large varices and the choice of treatment should be based on local resources and expertise, patient preference and characteristics, contraindications, and adverse events.²¹ The advantages of NSBBs are their low cost, ease of administration, no need for specific expertise, and no need for endoscopic monitoring. In addition, because NSBBs reduce the risk of first variceal bleeding by reducing the portal pressure, these drugs may prevent other complications of portal hypertension, such as ascites, SBP, and encephalopathy.^{114,115} The disadvantages of NSBBs are that around 15% of patients have contraindications and another 15-20% experience unpleasant side effects, such as shortness of breath, lethargy, fatigue, and pre-syncope, which require dose reduction or discontinuation.¹¹⁶ Furthermore, 25-40% of patients do not achieve a sufficient hemodynamic response for reduction of portal pressure and prevention of first variceal bleeding.¹¹⁷⁻¹¹⁹ In addition, treatment with NSBB need for lifelong therapy and the risk of variceal bleeding increases after the cessation of therapy.¹²⁰ The advantages of EBL are that it can be done in the same session as screening endoscopy and has few contraindications. In addition, the side effects are less frequent. A previous meta-analysis suggested that adverse events were associated with EBL in 42.7% and with NSBBs in 56.1%.¹¹³ While, the disadvantages of EBL are need for specific expertise and potential risk for lethal bleeding from post-procedure ulcers.²⁰ It is usually considered that even the frequency of adverse events is significantly lower with EBL, the severity of adverse events is greater with EBL. A previous meta-analysis suggested that fatal adverse events were significantly lower with NSBBs (RR, 0.14; 95% CI, 0.02-0.99).¹²¹ In addition, because EBL is a local therapy, it could not affect portal hypertension and could not prevent other complications by portal hypertension.¹²² Lastly, because recurrence rate after eradication by EBL is very high, periodic surveillance endoscopic follow-up is needed to detect recurrence of high-risk varices.¹¹⁵ A recent study evaluated the predicted preferences of patients and physicians for the primary prevention of variceal

bleeding and 64% of patients and 57% of physicians preferred EBL over NSBBs.¹²³

Theoretically, the combination of direct mechanical obliteration of varices by EBL and reduction of portal pressure by NSBBs would have a synergistic effect and would be more effective than either treatment alone. There have been several randomized controlled trials (RCTs)¹²⁴⁻¹²⁷ to compare the efficacy for primary prophylaxis between single treatment and combined treatment: two of them compared the efficacy of combined treatment with EBL alone^{124,125} and two RCTs compared combined treatment and NSBB alone.^{126,127} In two RCTs that compared combined treatment and EBL alone,^{124,125} the incidence of first variceal bleeding and mortality rate did not differ between two groups, while the incidence of variceal recurrence after eradication by EBL was significantly lower in the combined treatment group compared to EBL alone group.^{124,125} In the study by Sarin et al, the incidence of variceal bleeding (7% vs. 11%, $P=0.72$) and mortality rate (8% vs. 15%, $P=0.37$) within 20 months did not differ between combined treatment group and EBL only group, while the proportions of patients who achieved variceal eradication by EBL and those who achieved target heart rate or HVPG reduction were not provided and 11.8% of enrolled patients had noncirrhotic portal hypertension.¹²⁴ Similarly, the incidence of variceal bleeding (3% vs. 6%, $P=1.0$) and mortality rate (12% vs. 6%, $P=0.27$) within 1 year did not differ between two groups in another study by Bonilha et al.¹²⁵ Variceal eradication rate was 100% in this study, while the number of included patients was relatively small (32 patients in the EBL group and 34 patients in the combined group).¹²⁵ Among two RCTs comparing combined treatment and NSBB alone, one study suggested, that the incidence of variceal bleeding (14% vs. 13%, $P=0.90$) and mortality rate (22.9% vs. 21.4%, $P=0.22$) did not differ between two groups,¹²⁶ while variceal eradication rate was 71%, which was relatively lower than previous studies.¹¹³ In another RCT that comparing combined treatment and NSBB alone, although the incidence of VB was significantly lower in the combined treatment group compared to NSBB alone group (6% vs. 31%, $P=0.03$),¹²⁷ this study has major limitations of too small sample size and high incidence of variceal bleeding in the NSBB alone group. Thus, because most of studies showed no significant benefit of combined treatment compared with single treatment, current guidelines do not recommend combined treatment for primary prophylaxis. However, very recently, a large scale multicenter RCT was presented at the International Liver Congress of the European Association for the Study of the Liver on April, 2017.¹²⁸ In this study, 290 cirrhotic patients with medium or large varices with red

color sign without previous history of bleeding were randomized propranolol alone, EBL alone, and combined treatment. The proportions of patients who achieved EV eradication by EBL and who achieved target heart rate by propranolol were 84.1% and 77.7%, respectively. The incidence of variceal bleeding was significantly lower in the combined treatment group (3.4%) compared to the propranolol alone group (14%, $P=0.012$) and EBL alone group (14.9%, $P=0.008$) without difference in mortality rate within 2 years. In addition, numbers of EBL sessions and used rubber bands for EV eradication and EV recurrence rate after eradication by EBL were significantly lower in the combined treatment group in this study.¹²⁸ Because this well-designed large-scale RCT showed superiority of combined treatment for the primary prophylaxis, revision of recommendation of practice guidelines should be considered.

There have been several studies that evaluated the efficacy of carvedilol for the primary prophylaxis.^{24,129,130} In one RCT, the incidence of variceal bleeding was significantly lower in the carvedilol group than in the EBL group (13.4% vs. 24% within 24 months, $P=0.04$) without difference in mortality (28.5% vs. 27.9% within 24 months, $P=0.71$).¹²⁹ However, main limitations of this study are too low rate of achievement of variceal eradication (58%) and relatively higher rate of bleeding in the EBL group compared to other previous studies.¹¹³ While, in another RCT, the incidence of variceal bleeding (8.5% vs. 6.9% within 24 months, $P=0.61$) and mortality rate (19.5% vs. 12.8% within 24 months, $P=0.23$) did not differ between carvedilol and EBL groups.¹³⁰ In this study, variceal eradication was achieved in 75% of the EBL group, which is also slightly lower than other previous studies. In a previous meta-analysis, variceal eradication rate by EBL was 91.6%.¹¹³ In these two studies, hemodynamic response was not evaluated by HVPG measurement.^{129,130} A recent study evaluated the effect of carvedilol in patients with hemodynamic non-response to propranolol.²⁴ In this study, patients with EVs and HVPG >12 mmHg were treated with propranolol. After 4 weeks of propranolol treatment, HVPG measurement was repeated to evaluate the hemodynamic response to propranolol. Hemodynamic responders (decrease in HVPG $\geq 20\%$ from baseline or to <12 mmHg) to propranolol were kept on propranolol, while hemodynamic non-responders were switched to carvedilol. After 4 weeks of carvedilol treatment, HVPG measurement was repeated, and hemodynamic responders to carvedilol were kept on carvedilol, while carvedilol non-responders underwent EBL until variceal eradication. Hemodynamic responders to propranolol was 36% of all enrolled patients and 56% of propranolol non-responders achieved hemodynamic response to carvedilol. Incidence of vari-

ceal bleeding was significantly lower in the hemodynamic responders to propranolol (11%) or carvedilol (8%) than EBL-treated patients within 2 years (24%, $P=0.043$).²⁴ However, because this study included patients according to the HVPG (>12 mmHg) rather than to the size of EVs, 39% of enrolled patients have small sized EVs. Therefore, significant proportion of patients might not be indicated for primary prophylaxis. In addition, similar with the study by Tripathi et al.,¹²⁹ the incidence of VB in EBL group was higher than other previous studies.¹¹³ In summary, carvedilol could be added to the treatment options of primary prophylaxis, while superiority of carvedilol to EBL or to other NSBBs has not been confirmed yet. Carvedilol could be a good option in patients with high-risk EVs and intolerance or non-response to other NSBBs such as propranolol and nadolol.

Management of acute variceal bleeding

Although there has been significant improvement in survival of patients with acute variceal bleeding during several decades, mortality rate still remains high as 12-22%.¹⁴⁻¹⁶ Therefore, prompt and appropriate management is important in patients with acute variceal bleeding. The mainstay of the management of patients with acute variceal bleeding includes resuscitation, pharmacological treatment, and endoscopic treatment.

General management

In patients with acute bleeding of any cause, the first and most important step is the initial resuscitation for protection of the circulatory and respiratory status of the patient. Volume replacement should be initiated to restore and maintain hemodynamic stability. Regarding the packed red blood cell (PRBC) transfusion, a recent RCT showed a deleterious effect of over-transfusion.¹³¹ In this study, 889 patients with UGI bleeding was randomized to restrictive transfusion group (initiating PRBC transfusion at a hemoglobin threshold of 7 g/dL and maintaining it at 7-9 g/dL) and the liberal transfusion group (initiating PRBC transfusion at a hemoglobin threshold of 9 g/dL and maintaining it at 9-11 g/dL). Mortality rate (5% vs. 9%, $P=0.02$) and the incidence of serious adverse events (12% vs. 18%, $P=0.01$) were significantly lower in the restrictive transfusion group. In the subgroup analysis of patients with bleeding from GEV (220 patients, 23.6%), there was a trend of lower hemostasis failure rate (11% vs. 22%, $P=0.05$) and mortality rate (11% vs. 18%, $P=0.08$) in the restrictive transfusion group: mortality rate was significantly lower in the restrictive transfusion group among patients with Child-Pugh class A/B (4%

vs. 12%, $P=0.02$), while it did not differ between two groups among patients with Child-Pugh class C (38% vs. 41%, $P=0.91$). Improved survival in the restrictive transfusion group might be related to the reduced hemostasis failure and serious adverse events. Previous studies suggested that transfusion may counteract the splanchnic vasoconstrictive response caused by hypovolemia and, in turn, impair the formation of clots by increase in splanchnic blood flow and pressure.^{132,133} In addition, transfusion may induce coagulation abnormalities.^{134,135} Furthermore, restitution of blood volume by transfusion can induce rebound increase in portal pressure.^{136,137} Consistently, in 151 patients with bleeding from GEV who performed HVPG measurement at baseline and repeated at 2-3 days later, HVPG was significantly decreased in the restrictive transfusion group (from 20.5 ± 3.1 mmHg to 21.4 ± 4.3 mmHg, $P=0.03$), while there was no significant change in the liberal transfusion group, despite they were treated with intravenous somatostatin.¹³¹ Therefore, recent guidelines recommend PRBC transfusion at a target hemoglobin level between 7 and 9 g/dL.^{21,115}

There have been insufficient evidences supporting the routine use of clotting factors or platelet transfusion to improve hemostasis rate, prevent rebleeding and development of hepatic encephalopathy. In a recent meta-analysis, recombinant factor VIIa treatment reduced the 5-day treatment failure rate (17% vs. 26%, $P=0.049$) with a potential increased risk of arterial thrombo-embolic events in patients with EV bleeding.¹³⁸

Bacterial infection is frequent in cirrhotic patients with upper gastrointestinal bleeding^{139,140} and it is associated with an increased rate of failure to control bleeding,^{139,141} rebleeding,¹⁴² and hospital mortality.¹⁴¹ A recent meta-analysis showed that prophylactic antibiotics during an acute variceal bleeding reduce the risks of mortality (RR, 0.79; 95% CI, 0.63-0.98), mortality from bacterial infections (RR, 0.43; 95% CI, 0.19-0.97), bacterial infections (RR, 0.35; 95% CI, 0.26-0.47), and rebleeding (RR, 0.53; 95% CI, 0.38-0.74).¹⁴³ While, another recent study questioned about the usefulness of the routine use of antibiotic prophylaxis in Child-Pugh class A patients with acute variceal bleeding because of very low rate of infection (2%) and mortality (0.4%) in the absence of antibiotics.¹⁴⁴ However, this study was a retrospective analysis¹⁴⁴ and there were no prospective studies that evaluated the usefulness of antibiotic prophylaxis in these patients. Therefore, current guidelines recommend routine prophylactic antibiotics in all cirrhotic patients presenting variceal bleeding regardless of Child-Pugh class.^{21,115} In a previous RCT which compared intravenous ceftriaxone (1 g/day) and oral norfloxacin (400 mg twice daily) in the prophylaxis of bacterial infection in cirrhotic patients with GI

bleeding, incidences of proved or possible infections (11% vs. 33%, $P=0.003$), proved infections (11% vs. 26%, $P=0.03$), spontaneous bacteremia or spontaneous bacterial peritonitis (12% vs. 2%, $P=0.03$) were significantly lower in the ceftriaxone group.¹⁴⁵ However, this study included only patients with advanced cirrhosis (at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dL),¹⁴⁵ these results could not be applied to patients with variceal bleeding and less advanced cirrhosis. In addition, considering that 6 of 7 gram-negative bacilli in the norfloxacin group were quinolone resistant, most of the superiority of ceftriaxone was explained by a higher rate of infections by quinolone-resistant organisms.¹⁴⁵ Therefore, selection of prophylactic antibiotics should be based on local resistance patterns. Current guidelines recommend short-term (maximum 7 days) intravenous ceftriaxone 1 g/24 h as the best prophylactic antibiotics in patients with variceal bleeding.^{21,115}

Pharmacological treatment

Vasoactive drugs, such as vasopressin, terlipressin, somatostatin, and octreotide, are effective in hemostasis in patients with acute variceal bleeding by reducing portal pressure. Vasopressin reduces portal blood flow, portal systemic collateral blood flow, and intra-variceal pressure by induction of systemic and splanchnic vasoconstriction. However, due to the significant side effects including an increase in peripheral vascular resistance and reduction in cardiac output and coronary blood flow, it is not recommended in these days. The addition of nitroglycerine to vasopressin reduces in hemostasis failure and cardiovascular side effects.^{107,146} Terlipressin, a synthetic analogue of vasopressin, is also effective in the reduction of portal pressure and hemostasis of acute variceal bleeding. Among all kinds of vasoactive drugs, terlipressin is the only drug which has been proven to reduce mortality (RR=0.66, 95% CI 0.49-0.88),¹⁴⁷ while the efficacies for bleeding control and survival did not differ among terlipressin, somatostatin, and octreotide in another meta-analysis¹⁴⁸ and a recent large-scale RCT.¹⁴ Therefore, there is no preference when selecting one of several vasoactive drugs. Somatostatin reduces portal pressure and portal blood flow by induction of selective splanchnic vasoconstriction.¹⁴⁹ A meta-analysis showed that somatostatin and its analogue, octreotide, are as effective as terlipressin in patients with acute variceal bleeding.¹⁴⁸ In a recent meta-analysis, the use of vasoactive drugs in patients with acute variceal bleeding was associated with a significant reduction in 7-day mortality (RR, 0.74; 95% CI, 0.57-0.95) and significant increase in hemostasis rate (RR, 1.21; 95% CI, 1.13-1.30).¹⁴⁸ There-

fore, these drugs should be started as soon as possible, before endoscopy, in patients in whom VB is suspected.^{21,115} In patients with acute variceal bleeding, it is recommended that vasoactive drugs should be continued for 3-5 days,^{21,115} while, in a previous RCT, 30-day rebleeding (3.1% vs. 1.5%, $P=0.50$) and 30-day mortality (9.2% vs. 9.2%, $P=0.50$) did not differ between 24 hours and 72 hours of the duration of terlipressin treatment in patients with successful hemostrasis by EBL without advanced cirrhosis (Child-Pugh score ≥ 12).¹⁵⁰ In a previous study, serum sodium level was reduced ≥ 5 mEq/L in 67% and >10 mEq/L in 36% of cirrhotic patients during terlipressin treatment.¹⁵¹ Therefore, sodium level should be monitored during terlipressin treatment.²¹ Higher baseline serum Na level,^{151,152} lower Child-Pugh or MELD score,^{151,152} and lower body mass index¹⁵² were associated with the development of terlipressin-induced hyponatremia.

Endoscopic treatment

Endoscopy should be performed as soon as possible to evaluate the source of bleeding. If a source of bleeding is confirmed as variceal bleeding, endoscopic treatment should be performed. EBL is the endoscopic treatment of choice for patients of acute bleeding from EVs and should be performed when EVs are confirmed or suspected as a source of bleeding on endoscopy. EIS is no longer recommended as standard treatment for acute bleeding from EVs because of higher incidence of treatment failure, mortality, and adverse events compared to EBL. A meta-analysis showed EBL reduced incidences of rebleeding (RR, 0.47; 95% CI, 0.29-0.78), mortality (RR, 0.67; 95% CI, 0.46-0.98), and esophageal strictures (RR, 0.10; 95% CI, 0.03-0.29).¹⁵³ EBL should be combined with vasoactive drugs. A previous meta-analysis showed that combination of endoscopic treatment (EIS or EBL) and vasoactive drugs improved initial hemostasis (RR, 1.12; 95% CI, 1.02-1.23) and reduced early rebleeding within 5 days (RR, 1.28; 95% CI, 1.18-1.39) compared to endoscopic treatment alone.¹⁵⁴ EVO is not recommended for the treatment of bleeding from EVs because EVO showed no difference in the hemostasis rate, higher rebleeding rate, and potential risk of systemic embolization.¹⁵⁵

Regarding the optimal time for endoscopy in patients with suspected variceal bleeding, most guidelines recommend that endoscopy should be performed within 12 hours of presentation,^{21,115} while there is no evidence to support this time limitation. A previous retrospective study suggested that delayed endoscopy (>15 hours after admission) was one of the independent risk factors of in-hospital mortality.¹⁵⁶ Similarly, in a prospective observational study, 6-week rebleeding rate (18.9% vs. 38.9%, $P=0.028$) and

mortality (27% vs. 52.8%, $P=0.031$) were lower in patients with early endoscopy (≤ 12 hours) than those with delayed endoscopy (>12 hours).¹⁵⁷ However, because these two studies were not performed as randomized controlled design, many confounding factors might have influenced the results, such as the unstable hemodynamics which could cause delayed endoscopy as well as poor prognosis. Therefore, optimal timing of endoscopy in patients with suspected variceal bleeding could not be confirmed until a large-scale RCT would be performed. In another retrospective study, time of endoscopy was not associated with prognosis in patients who present with hemodynamically stable variceal bleeding.¹⁵⁸

Early TIPS in high-risk patients

TIPS has been considered as a salvage treatment in patients with VB who failed control of bleeding. However, recent studies suggested that early TIPS is useful in patients with bleeding from EVs and high-risk of treatment failure.^{19,159} In one study, early TIPS (within 24 hours after admission) significantly reduced treatment failure (12% vs. 50%, $P<0.001$), in-hospital mortality (11% vs. 38%, $P<0.02$), and 1-year mortality (11% vs. 31%, $P<0.05$) in high-risk EV bleeding patients.¹⁹ In this trial, EIS was used as standard endoscopic treatment,¹⁹ which is not recommended as standard treatment. Consistently, early TIPS (within 72 hours after randomization) significantly reduced treatment failure (3% vs. 45%, $P=0.001$) and 1-year mortality (14% vs. 39%, $P<0.001$) in another study.¹⁵⁹ In both studies, early TIPS did not increase the risk of hepatic encephalopathy.^{19,159} However, as followed observational studies could not confirmed beneficial effect on survival of early TIPS,^{160,161} further studies are needed to confirm the role of early TIPS in patients with high-risk patients. In addition, reestablishment of the criteria of the high-risk patients is also needed.²¹ Actually, different definitions of high-risk patients were used in two previous RCTs: it was defined as HVPG >20 mmHg in one study¹⁹ and as Child-Pugh class cirrhosis with a score 10-13 and those with Child-Pugh class B with active bleeding on endoscopy despite intravenous vasoactive drug therapy in another study.¹⁵⁹ These definitions have no evidence and it has been suggested that these criteria may overestimate the risk of treatment failure in some patients: patients with Child-Pugh class B treated with the standard care for EV bleeding usually have better prognosis than those with Child-Pugh class C.^{162,163}

Management of patients with failure to hemostasis

Placement of TIPS is considered a best salvage therapy for pa-

tients with standard treatment failure. In previous studies, salvage TIPS achieved control of bleeding in 90-100% with low rebleeding rates of 6-16%.¹⁶⁴ Balloon tamponade is effective in control of acute EV bleeding in up to 90% of cases, while rebleeding rate after deflation is high as about 50%.^{165,166} In addition, because it is associated with serious complications such as esophageal ulceration, esophageal rupture, and aspiration pneumonia,¹⁶⁷ the placement of balloon tamponade should not exceed 24-48 hours.¹⁶⁷ Therefore, balloon tamponade is usually used as a bridge to more definitive therapy, such as TIPS. A recent small RCT suggested a self-expandable, esophageal covered metal stent as an alternative to balloon tamponade.¹⁶⁸ In this study, primary endpoint, defined as survival to day 15, control of bleeding, and absence of serious adverse events, was more frequently achieved in the stent group (66% vs. 20%, $P=0.025$) with higher rates of hemostasis (85% vs. 47%, $P=0.025$) without improvement in survival in 28 patients with EVB refractory to standard medical and endoscopic treatment.¹⁶⁸ This stent can be placed endoscopically without radiological guidance and removable. In addition, it can stay in place for up to 2 weeks.

Secondary prophylaxis

In patients who survive an acute variceal bleeding, varices rebleed in 60% in the first year with high mortality rate of up to 33%.¹²² Therefore, appropriate treatment for the prevention of variceal rebleeding is very important.

NSBBs are the first drug that has been used for prevention of variceal rebleeding and various studies showed significant reduction of rebleeding rate with NSBBs compared to the placebo.¹⁶⁹⁻¹⁷¹ The combination of ISMN and NSBBs enhances the portal pressure-reducing effect.¹⁷² However, the addition of ISMN increases the frequency of side effects such as headache and lightheadedness. In a previous RCT to compare the efficacy of ISMN+PPL and PPL alone, rebleeding was significantly lower in the ISMN+NSBB group (RR, 0.51; 95% CI, 0.28-0.95), while the incidence of discontinuation by adverse events was also higher in this group (15.2% vs. 2.0%, $P=0.03$).¹⁷³ However, rebleeding rate did not differ between two groups with a higher rate of side effects in the ISMN+NSBB group in a meta-analysis.¹⁷⁴ This combined drug therapy has been shown to be superior to EIS. In a previous RCT, the incidences of rebleeding (25% vs. 55% within 2 years, $P=0.002$) and treatment-related complications (16.3% vs. 37.2%) were significantly lower in the ISMN+NSBB group compared to the EIS group without difference in survival rate.¹⁷⁵ Compared to EBL, the rebleeding rate was higher¹⁷⁶ or not different^{111,177} with

this combined drug therapy in meta-analyses. Mortality rate was significantly higher in the ISMN+NSBB group (RR, 1.25; 95% CI, 1.01-1.55) in one meta-analysis,¹¹¹ while it did not differ between two groups (RR, 0.81; 95% CI, 0.61-1.08) in another meta-analysis.¹⁷⁷ In a long-term follow-up study, ISMN+NSBB treatment showed lower mortality rate (30% vs. 49%, $P=0.013$), while rebleeding rate was higher in this group (64% vs. 30%, $P=0.001$) compared to the EBL group.¹⁷⁸ Addition of these combined drug therapy to the EBL did not reduce the rebleeding rate compared to the EBL alone in a RCT (27% vs. 31% within 2 years, $P=0.822$)¹⁷⁹ and meta-analysis (RR, 0.57; 95% CI, 0.31-1.08).¹⁷⁶ Similarly, rebleeding rate did not differ between the ISMN+NSBB+EBL group and ISMN+NSBB group in the previous RCTs^{180,181} and a meta-analysis (RR, 0.76; 95% CI, 0.56-1.03).¹⁷⁶

Until EBL is used for the treatment of GEV, EIS plus NSBBs was the first-line treatment for the prevention of rebleeding.^{107,182} However, with the superior efficacy and safety to EIS, EBL is considered as an endoscopic treatment of choice for secondary prophylaxis. In a meta-analysis, EBL reduced the rebleeding rate (40.4% vs. 57.4% within 2 years, $P=0.09$; RR, 0.52; 95% CI, 0.37-0.74), mortality rate (RR, 0.67; 95% CI, 0.46-0.98), and the incidence of esophageal strictures (RR, 0.1; 95% CI, 0.03-0.29) compared to EIS.¹⁵³ Adding EIS to EBL has no additional beneficial effects as compared with EBL alone.^{183,184}

Currently, the first-line therapy for secondary prophylaxis is the combination of NSBBs plus EBL. Addition of NSBBs to EBL may act synergistically, because it could prevent rebleeding before variceal eradication by EBL and also could prevent variceal recurrence after eradication. Several RCTs showed that significantly lower rebleeding rate in the combination treatment group compared to the EBL alone.^{185,186} Consistently, rebleeding rate was significantly lower with a combination treatment than single treatment with EBL (RR, 0.68; 95% CI, 0.52-0.89) or NSBBs (RR, 0.71; 95% CI, 0.59-0.86) in a meta-analysis.¹⁸⁷ However, in another meta-analysis, although combination treatment significantly reduced rebleeding compared to the EBL alone (RR, 0.44; 95% CI, 0.28-0.69), the benefit of this treatment was only marginal compared to the pharmacological therapy (RR, 0.76; 95% CI, 0.58-1.00).¹⁸⁸ This result suggests that NSBBs are the cornerstone of secondary prophylaxis and other treatment, such as TIPS, should be considered in NSBBs-intolerant patients, rather than single treatment with EBL. In patients in whom EBL is not available, addition of ISMN to NSBBs to maximize portal pressure lowering effect could be considered.⁵

Recent several RCTs evaluated the efficacy of carvedilol for sec-

ondary prophylaxis.^{189,190} The incidences of rebleeding (29.3% vs. 42.2% within 2 years, $P=0.857$) and mortality (23.0% vs. 38.3%, $P=0.110$) did not differ between the carvedilol and EBL alone groups.¹⁸⁹ Another study compared the efficacy of carvedilol to ISMN+NSBB and showed no difference in the incidence of rebleeding (61% vs. 62%, $P=0.90$) and rebleeding from EVs (51% vs. 43%, $P=0.43$).¹⁹⁰ However, in both studies, carvedilol was not compared to the current standard of care, combination of EBL and NSBBs, and more data are needed to recommend carvedilol for secondary prophylaxis. In addition, carvedilol may decrease arterial pressure²² and its use should be avoided in patients with refractory ascites.¹⁹¹

In a recent multicenter RCT, addition of simvastatin to the standard treatment for prevention of variceal rebleeding, EBL plus NSBBs, did not reduce the rebleeding rate (25% in the simvastatin group vs. 28% in the placebo group, $P=0.699$), while it significantly reduced the mortality rate (9% vs. 22%, $P=0.030$).¹⁹² The improvement in mortality in the simvastatin group was mainly related to a decrease in liver-related deaths (absolute risk reduction, 10.4%; 95% CI, 0.26%-20.5%).¹⁹² While, two episodes of symptomatic rhabdomyolysis were reported in the simvastatin group. Both patients had poor liver function at baseline with a bilirubin level >5 mg/dL and it suggested that patients with severely deteriorated liver function might develop rhabdomyolysis at lower doses than the general population. This calls for a close monitoring of muscle enzymes in this particular group of patients, and for testing either atorvastatin or lower doses of simvastatin in future studies including patients with advanced cirrhosis.¹⁹²

TIPS is considered as a treatment of choice in patients who have rebleeding despite first-line secondary prevention with EBL plus NSBBs. In a recent RCT, rebleeding rate was lower the TIPS group (7% vs. 26%) with a higher incidence of encephalopathy compared to the ISMN+NSBBs group.¹⁹³

MANAGEMENT OF GASTRIC VARICES

In a previous study, prevalence of GVs in patients with portal hypertension regardless of the etiology was 25.9% and it was 21.6% in 301 of 568 patients (53%) who had cirrhosis-induced portal hypertension.¹⁹⁴ In another study, 25.1% of patients with cirrhosis had GVs, which was lower than the prevalence of EVs of 57%.¹⁹⁵ Bleeding occurs less frequently in GVs compared to EVs: GV bleeding accounts for 14-36% of acute variceal bleeding.^{166,196,197} However, once bleeding occurs, patients with GV

bleeding have a poorer prognosis and are associated with a requirement of more transfusions and higher rebleeding and mortality rates than those with EV bleeding.^{194,198,199} In a previous prospective study, the incidence of GV bleeding was 16%, 36%, and 44% at 1, 3, and 5 years, respectively, in patients with cirrhosis and fundal varices (GOV2, 29.5%; isolated gastric varices 1 [IGV1], 70.5%).¹⁹⁵ The size of varices, presence of red color sign, and the degree of liver function were independent predictive factors for GV bleeding.¹⁹⁵

Classification of GVs

Sarin's classification is the most commonly used, because it is useful for risk stratification and management of GVs.¹⁹⁴ Firstly, GVs are divided into GOV and IGV according to the association of GVs with EVs. And then, GOV and IGV are divided into GOV1/GOV2 and IGV1/IGV2, respectively, according to their location within the stomach. GOV1 appears as continuations of EVs and extend for 2-5 cm below the gastroesophageal junction, along the lesser curvature of the stomach, while GOV2 extend below gastroesophageal junction into the fundus of the stomach. IGV1 is located in the fundus of the stomach and IGV2 is located anywhere in the stomach or intestine as isolated ectopic varices. GOV2 and IGV1 are also called as fundal varices. Hemodynamically, GOV1 and EVs are supplied mainly from the left and right gastric veins, while GOV2 and IGV1 are frequently supplied from the short and posterior gastric veins.⁷³ IGV2 is caused by dilation of branches of the gastroepiploic veins.²⁰⁰

In a previous study, GOV1 was the most common subtype of GVs (14.9% of patients with portal hypertension) followed by GOV2 (5.5%) in patients with portal hypertension. The prevalence of IGV1 and IGV2 were 1.6% and 3.9%, respectively.¹⁹⁴ While the bleeding incidence is higher in the fundal varices (78% for IGV1 and 55.1% for GOV2) than GOV1 (11.8%) and IGV2 (9.1%).¹⁹⁴ However, although the bleeding risk is not high in GOV1, because of the highest prevalence, GOV1 is the most common site of GV bleeding (55-67% in GOV1, 24-29% in GOV2, 9-20% in IGV1, and 0-2.3% in IGV2).^{44,201,202}

GVs vs. EVs

There are several differences in the characteristics between EVs and GVs, which could affect the treatment efficacy by some modalities. Firstly, GVs usually lie much deeper within the submucosa than EVs.²⁰³ Therefore, thicker underlying submucosal layer of GVs

could lead partial ligation of varices by EBL, which could lead fatal bleeding after the detachment of the band.²⁰⁴⁻²⁰⁶ Secondly, variceal size is usually larger in GVs compared to EVs, which also could be a cause of partial ligation by EBL. EBL is usually not recommended for large varices (diameter >2 cm) because of the limited diameter of the ligator.²⁰⁷ Thirdly, GVs are continuously exposed to gastric acid and pepsin.²⁰⁸ Therefore, the incidence of bleeding from EBL-induced ulcers may be more frequent in the stomach than in the esophagus.²⁰⁹ Fourthly, peristalsis of the stomach may lead sloughing of ligated tissue by EBL.⁴⁴ Fifthly, large spontaneous gastrorenal shunts are more frequent in GVs (60-85% of cases)^{73,210} than EVs (17-21% of cases)⁷³ and the blood of these shunts is fast and abundant.²¹¹ Because sclerosing agent of EIS escape into the systemic circulation rapidly through these shunt, EIS is not effective for the management of GVs. In addition, this large shunts could compete with the TIPS as a porto-systemic blood outflow pathway. Therefore, most of the blood flow might remain in GVs even after creation of TIPS with unchanged high risk of bleeding. Lastly, probably because of the presence of large spontaneous gastrorenal shunts in GVs, the mean portal pressure in patients with GVs is usually lower than in those with EVs.⁷³ Therefore, NSBBs or TIPS may be less effective for GVs than EVs.

Primary prophylaxis

There is only one RCT on the primary prophylaxis against fundal variceal bleeding which compared the efficacy of NSBBs, EVO, and no treatment.²¹² In this study, 89 patients with cirrhosis and large (≥ 10 mm in size) fundal varices (GOV2, 85.4%; IGV1, 14.6%) were randomized to EVO, NSBBs, or no treatment and the cumulative GV bleeding rate over a median follow-up of 26 months was significantly lower in the EVO group (13%) than in the NSBBs group (28%, $P=0.039$) and no-treatment group (45%, $P=0.003$) without significant difference between the NSBBs and no-treatment groups ($P=0.374$).²¹² Although this study suggested the superior efficacy of EVO, further studies are needed to evaluate the risk and benefit ratio to recommend EVO for the primary prophylaxis. In addition, the role of NSBBs for primary prophylaxis against GV bleeding is questionable. Although several previous studies suggested that BRTO is very effective in the primary prophylaxis in patients with fundal varices,^{82,213} prospectively designed, larger-scale, randomized trials are needed for the recommendation. Because there are no studies evaluated the efficacy of TIPS in this setting and considering the adverse events by TIPS such as increased incidence of hepatic encephalopathy, TIPS is not

recommended.¹¹⁵

Most guidelines recommend that primary prophylaxis for GOV1 follow the recommendations for EVs.¹¹⁵ because GOV1 could disappear after the treatment of EVs. This recommendation is based on the previous studies which showed disappearance of GOV1 in 59% of patients within 6 months after EIS for EVs.¹⁹⁴ However, currently recommended treatment for EVs is EBL, rather than EIS and action mechanisms of two procedures are quite different. Because mechanical strangulation is the main mechanism for the eradication of EVs in EBL, treatment effect is usually limited to the mucosa and submucosa, while, because the main mechanism for EIS is the chemical reaction which leads to fibrosis, the effects of EIS could extend into the deeper layers and perforating veins. In addition, sclerosant flows in a caudal direction towards the GOV1.²¹⁴⁻²¹⁶ Therefore, EIS could obliterate GOV1 also, which is associated with EVs, while the effect of EBL for EVs on the GOV1 is not clear. In a recent retrospective study that evaluated the changes of GOV1 after eradication of EVs by EBL, GOV1 disappeared in 64.7% of patients,²¹⁷ which was comparable to the disappearance of GOV1 after EIS for EVs in the previous study.¹⁹⁴

In summary, until now, there is no recommendation for patients with fundal varices that have not bleed.¹¹⁵ In patients with GOV1 without previous history of bleeding, GOV1 could disappear after the eradication of EVs by EBL.

Bleeding control

The endoscopic treatment of choice for bleeding from GVs is EVO. Various studies showed more than 90% of success rate in the initial hemostasis^{201,218-221} and 22-37% of rebleeding rate.^{201,218,219} In a previous retrospective study to evaluate long-term outcome of patients treated with EVO for GV bleeding, initial hemostasis rate was 96.2% and rebleeding rates at 1, 5, and 10 years were 35.3%, 47.3%, and 51.8%, respectively.²²²

Several RCTs compared the efficacy of EVO and EBL for bleeding from GVs. In the first study which was performed with 60 patients with GV bleeding (GOV1, 68.3%; GOV2, 23.3%, and IGV1, 8.3%), EVO showed significantly higher hemostasis rate (87% vs. 45%, $P=0.03$) and significantly lower rebleeding rate (31% vs. 54%, $P<0.001$).⁴⁴ In the second study which was performed with 97 patients with GV bleeding (GOV1, 54.6%; GOV2, 25.8%; and IGV1, 19.6%), although hemostasis rate was comparable between two groups (93.3% in both group, $P=1.000$), rebleeding rate was significantly lower in the EVO group (22.4% vs. 43.8%, $P=0.044$).²⁰¹ Third study was performed with 37 patients with

bleeding from GVs (GOV1, 59.5%; GOV2, 40.5%, and IGV1, 0%) and although success rate in initial hemostasis did not differ between EBL and EVO groups (88.9% vs. 100%; $P=0.43$), rebleeding rate was significantly higher in the EBL group (72.2% vs. 31.6%, $P=0.03$).²²³ A recent meta-analysis suggested the significantly higher hemostasis rate (RR, 4.44; 95% CI, 1.14-17.30; $P=0.032$) and significantly lower GV recurrence (RR, 0.26; 95% CI, 0.11-0.61; $P=0.002$) and rebleeding (RR, 0.33; 95% CI, 0.18-0.60; $P=0.0004$) rates in the EVO group compared to the EBL group.²²⁴

Before the introduction of EBL and EVO, EIS was used to control acute bleeding from GVs.¹⁹⁹ Some authors suggested high success rates for immediate hemostasis, but they also showed high rebleeding rates.^{199,225} Currently, EIS is not recommended for bleeding from GVs. In a retrospective study which compared EVO and EIS for bleeding from GVs, EVO showed significantly higher hemostasis rate (100% vs. 52.4%, $P<0.01$) and significantly lower rebleeding rate (1-year rebleeding rate, 7.6% vs. 76.6%, $P<0.01$).²²⁶ Although there was only a trend toward higher hemostasis rate in the EVO group compared to EIS group in a previous RCT (89% vs. 62%, $P=NS$), this analysis was performed with only 17 patients (8 in EIS group and 9 in EVO group) who had acute bleeding.²¹⁸

Although several retrospective studies suggested high efficacy of TIPS in patients with acute bleeding from GVs,^{227,228} there is no RCT evaluating the efficacy of TIPS for initial hemostasis in patients with GV bleeding. Considering the side effects, costs, and the requirement of equipment and experienced radiologists, TIPS is not recommended as first-line treatment for GV bleeding. Rather, TIPS could be a good option in patients with GV bleeding refractory to pharmacological and endoscopic treatments. In several studies evaluating the efficacy of "salvage" TIPS for refractory GV bleeding, hemostasis rate was 90-96%.^{227,228} BRTO also could be a good option in this condition with high treatment success rate of 95-100%.^{229,230}

GOV1 shows both characteristics of EVs and fundal varices. Characteristics of GOV1 similar with EVs are the size and the route of portal blood flow to the varices, while characteristics of GOV1 similar with fundal varices is the location. GOV1, similar with EVs, is supplied from the left and right gastric veins, while fundal varices (GOV2 and IGV1) are frequently supplied from the short and posterior gastric veins.⁷³ The size of GOV1 is usually smaller than that of fundal varices, much more similar with EVs. Therefore, current guidelines recommend both EBL and EVO for GOV1 bleeding. However, GOV1 is located in the stomach, the same location as with fundal varices, where the underlying sub-

mucosal layer is thicker than that in the esophagus. Thicker underlying submucosal layer of GVs could lead partial ligation of varices by EBL, which could lead fatal bleeding after the detachment of the band.²⁰⁴⁻²⁰⁶ In addition, stomach is continuously exposed to gastric acid and pepsin.²⁰⁸ Therefore, the incidence of bleeding from EBL-induced ulcers may be more frequent in the stomach than in the esophagus.²⁰⁹ These characteristics could increase the risk of treatment failure by EBL. Two RCTs showed similar efficacy between EBL and EVO for treating GOV1 bleeding,^{201,231} another RCT showed a trend toward higher hemostasis rate in the EVO group compared to the EBL group (85% vs. 43%, $P=0.08$).⁴⁴ Furthermore, a recent meta-analysis suggested the superior efficacy of EVO compared to EBL for the prevention of rebleeding from GOV1 (RR, 0.39; 95% CI, 0.16-0.94; $P=0.035$).²²⁴ A retrospective study showed a higher incidence of post-treatment ulcer bleeding and higher mortality rates in the EBL group as compared to those in the EVO group.²⁰⁹ In addition, a recent retrospective study showed significantly lower rebleeding rate (2-year rebleeding rate, 3.6% vs. 41.4%, $P=0.004$) and a trend toward lower mortality rate in the EVO group compared to the EBL group (2-year mortality rate, 6.9% vs. 25.8%, $P=0.050$).²³²

In summary, EVO is recommended for bleeding from fundal varices (GOV2 and IGV1). In patients with bleeding from GOV1, EVO is preferred than EBL. TIPS or BRTO could be considered in patients with refractory fundal varices.

Secondary prophylaxis

EVO is one of options for secondary prophylaxis. For this purpose, EVO should be repeated until complete obturation of GVs is achieved. In various studies which evaluated the long-term effect of EVO for GV bleeding, rebleeding rate was 8.0-29.2%.²³³⁻²³⁹ In a recent retrospective study with 91 patients who were treated with EVO for GV bleeding (GOV1, 22.0%; GOV2, 38.5%; and IGV1, 28.6%), the 1- and 2-year GV rebleeding rates were 11.0% and 21.3%, respectively. GV rebleeding rates were significantly higher in GOV2 (22.7% and 43.8%, respectively) compared to GOV1 (3.7% and 12.5%, respectively) and IGV1 (5.0% and 5.0%, respectively).²⁴⁰

A previous RCT compared the efficacy of EVO and NSBBs for secondary prophylaxis after achievement of hemostasis by EVO.²⁴¹ The 6-week rebleeding rate (23.8% vs. 15.0%, $P=NS$) and mortality rate (14.3% vs. 30.0%, $P=NS$) did not differ between the EVO and NSBBs groups. However, the sample size of this study was relatively small ($n=41$). In addition, only 25% of patients had

bleeding from GVs and 75% of patients with bleeding from EVs were treated with EVO.²⁴¹ In a more recent RCT, rebleeding rate (15% vs. 55%, $P=0.004$) and mortality rate (3% vs. 25%, $P=0.026$) were significantly lower in the EVO group than in the NSBBs group in patients with successful hemostasis with EVO for fundal variceal bleeding.²⁴² In another RCT, 95 patients with fundal variceal bleeding, which was successfully controlled with EVO, were randomized to EVO alone group or EVO plus NSBBs group.²⁴³ Rebleeding rate (22.9% vs. 23.4% at 1 year, $P=0.336$) and mortality rate (16.7% vs. 21.3%, $P=0.936$) did not differ between the EVO alone and EVO plus NSBBs groups.²⁴³ These studies suggest that NSBBs have no role in the secondary prophylaxis in patients with fundal varices.

A previous RCT compared EVO and TIPS for secondary prophylaxis. In this trial, 72 patients with GV bleeding (GOV1, 50.0%; GOV2, 45.8%; and IGV1, 4.2%) were randomized to repeated EVO or TIPS placement after hemostasis with EVO.²⁴⁴ Significant GV rebleeding rate was significantly lower in the TIPS group than in the EVO group (11% vs. 38%, $P=0.014$) with significantly higher incidence of hepatic encephalopathy in the TIPS group (25.7% vs. 2.7%, $P<0.01$).²⁴⁴ Survival rate did not differ between two groups (2-year survival rate, 70% in the TIPS group vs. 83% in the EVO group, $P=0.17$).²⁴⁴ Although this study suggested the superior efficacy of TIPS to EVO for prevention of rebleeding from GVs, considering the high incidence of encephalopathy and no difference in mortality rate, further studies are needed to recommend TIPS for secondary prophylaxis. In addition, rebleeding rate in the EVO group in this study was slightly higher compared to other studies. Especially, rebleeding occurred in 11 of 17 patients (65%) with bleeding from GOV1,²⁴⁴ which is usually smaller and shows better treatment response compared to bleeding from GOV2 or IGV1.

Various studies suggested that BRTO is very safe and effective in the management of GVs with high technical success (77-100%) and complete GV obliteration (82-100%) rates.²⁴⁵ A previous study showed very low 5-year GV recurrence (2.7%) and bleeding (1.5%) rates after BRTO in patients with fundal varices.²⁴⁶ In this study, EV worsening rates at 1, 3, and 5 years were 27%, 58%, and 66%, respectively.²⁴⁶ In another retrospective study, 5-year GV rebleeding rate after BRTO was 2.4% and the occurrence rates of high-risk EVs at 1 and 5 years were 8.6% and 17.6%, respectively.²²¹ In a recent meta-analysis, technical success rate, clinical success (defined as no recurrence of GV bleeding or complete obliteration of GV) rate, and EV recurrence rate was 96.4%, 97.3%, and 33.3%, respectively.⁷⁸ In a recent prospective non-

randomized trial compared the efficacy of EVO and BRTO for the prevention of GV bleeding in patients with GV bleeding or high-risk GVs, GV bleeding rate was significantly lower in patients treated with BRTO (15.4%) compared to those treated with EVO (71.4%, $P < 0.01$).²⁴⁷ However, GV bleeding rate was too high in the EVO group in this study (more than 50% of patients within 1 year).²⁴⁷

In summary, in patients who have recovered from GV bleeding, secondary prophylaxis with repeated EVO or BRTO could be recommended. TIPS could be considered as an option in patients with good liver function and are not feasible for EVO or BRTO.

SUMMARY

Variceal bleeding is still a serious complication in patients with liver cirrhosis and portal hypertension. Even with appropriate pharmacological and endoscopic treatment, mortality rate still remains high as 15-20%. Although several studies evaluated the efficacy of NSBBs for the prevention of development or aggravation of varices, results are controversial. Therefore, there is no recommendation in patients with cirrhosis without varices or with low-risk small varices. In patients with large EVs, although EV eradication by EBL is recommended, while EBL plus NSBBs is more effective in the primary prophylaxis against EV bleeding in a very recent RCT. In patients who have survived from EV bleeding, EBL plus NSBBs is recommended. Although there have been several data regarding the role of carvedilol in the prevention of development or aggravation of varices and primary and secondary prophylaxis, further studies are needed to confirm the effect of carvedilol. Until now, there is no recommendation for patients with fundal varices that have not bleed. In patients with GOV1 without previous history of bleeding, GOV1 could disappear after the eradication of EVs by EBL. EVO is recommended for bleeding from fundal varices. In patients with bleeding from GOV1, EVO is preferred than EBL. TIPS or BRTO could be considered in patients with refractory fundal varices. In patients who have recovered from GV bleeding, secondary prophylaxis with repeated EVO or BRTO could be recommended. TIPS could be considered as an option in patients with good liver function and are not feasible for EVO or BRTO.

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Conflicts of Interest

The author has no conflicts to disclose.

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