Gastrointestinal Bleeding

Incidence, etiology, role of drugs and outcome

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Thesis for the degree of Philosophiae Doctor

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Blæðingar frá meltingarvegi

Nýgengi, orsakir, tengsl lyfja og horfur

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"He among you is the wisest who knows
that his wisdom is really worth nothing at all"

Socrates

Ágrip

Blæðing frá meltingarvegi (*e. gastrointestinal bleeding – GIB)* er algeng ástæða innlagnar á spítala og tilvísunar til maga- og/eða ristilspeglunar. Ákveðin lyf eru talin tengjast GIB þó tengsl lyfja og ákveðinna tegunda eða orsaka blæðinga séu óljós. Horfur sjúklinga sem blæða frá meltingarvegi virðast vera góðar en skortur er á rannsóknum sem fylgja þessum sjúklingum eftir til lengri tíma.

Markmið þessa lokaverkefnis var að kanna nýgengi GIB sem og orsakir blæðinga. Einnig var markmið að kanna tengsl lyfja við slíkar blæðingar og hverjar skamm- og langtímahorfur þessara sjúklingar eru. Að lokum var markmið að rannsaka hversu margir af öllum þeim sem greinast með ristil- eða endaþarmskrabbamein á Íslandi eru með blæðingartengd einkenni og kanna hvað einkennir þann sjúklingahóp.

Heildarþýði þessa lokaverkefnis tók til allra sjúklinga sem fóru í maga- og/eða ristilspeglun á Landspítala árið 2010 sem og allra þeirra sem fóru í ristilspeglun á sömu stofnun árið 2013. Ábendingar og niðurstöður speglana voru skráðar á framsýnan hátt. Hjúkrunarfræðingar á speglunardeild skráðu lyfjasögu sjúklinga fyrir speglun. Lyfjasaga var bætt frekar með tvennum hætti, annars vegar var farið í gegnum sjúkraskrár sjúklinga, hins vegar voru upplýsingar frá Lyfjagagnagrunni Landlæknis notaðar til þess að kanna lyfjanotkun sjúklinga. Sjúklingum var skipt í fjögur megin þýði: Sjúklingar með bráða blæðingu frá efri hluta meltingarvegar (*e. acute upper gastrointestinal bleeding – AUGIB)* árið 2010, sjúklingar með bráða blæðingu frá neðri hluta meltingarvegar *(e. acute lower gastrointestinal bleeding – ALGIB)* árið 2010, sjúklingar með ALGIB bæði 2010 og 2013, að lokum sjúklingar með óútskýrða GIB árið 2010. Sjúklingar með óútskýrða blæðingu voru flokkaðir í sjúklinga með óútskýrða sýnilega GIB, sjúklinga með óútskýrða leynda GIB, sjúklinga með GIB þar sem uppruni blæðingar fannst ekki eftir hefðbundna uppvinnslu *(e. obscure GIB)*, að lokum sjúklinga með klíníska grun um GIB. Sjúklingum með óútskýrða blæðingu var fylgt eftir í a.m.k. þrjú ár. Viðmiðunarhópur var valin úr hópi þeirra sem fóru í maga- eða ristilspeglun á sama tímabili og voru ekki grunaðir um GIB, þeir voru paraðir við blæðara með tilliti til kyns og aldurs (±5 ár). Auk þeirra sem fóru í maga- eða ristilspeglun voru allir sjúklingar sem greindust með ristil- eða endaþarmskrabbamein á Íslandi á árunum 2008-2011 fundnir með hjálp Krabbameinskrár og sjúkrarskrár þeirra skoðaðar með tilliti til blæðingatengdra einkenna.

Algengustu ástæður AUGIB voru maga- og/eða skeifugarnarsár (40%), Mallory-Weiss rifur (12%) og vélindabólga (10%). Nýgengi AUGIB var 87/100.000 íbúa á Höfuðborgarsvæði á ári og jókst nýgengið með aldri. Þau lyf sem tengdust AUGIB voru bólgueyðandi gigtarlyf sem ekki eru sterar (e. Non-steroidal anti-inflammatory drugs –

NSAID) (p = 0,0002), hjartamagnýl (p = 0,0371) og kóvar (p = 0,0069). Notkun NSAID var einnig tengd klínískt marktækri AUGIB (líkindahlutfall (OR) = 6,6). Fæstir þeirra með AUGIB fóru í skurðaðgerð vegna blæðingar (1.9%) og dánartíðni var lág (1.3%). Algengustu ástæður ALGIB voru ristilpokar (23%), blóðþurrð í ristli og langvinnir bólgusjúkómar í þörmum (*e. inflammatory-bowel disease – IBD)*. Nýgengi ALGIB var einnig 87/100.000 íbúa á Höfuðborgarsvæði á ári og jókst með aldri. Eftirfarandi lyf tengdust ALGIB: NSAID (OR 3,5), hjartamagnýl (OR 1,5) og kóvar (OR 2,8). Þeir sem voru með blæðingu frá ristilpokum voru líklegri en viðmið til þess að nota NSAID, (OR 8,8), hjartamagnýl (OR 2,0) og kóvar (OR 2,7). Þeir sem voru með blóðþurrð í ristli voru líklegri en viðmið til þess að nota hjartamagnýl (OR 2,3) og þeir með IBD voru líklegri til þess að nota NSAID (OR 3,4). Sjúklingar með klínískt marktæka ALGIB voru líklegri en viðmið til þess að nota NSAID (OR 2,0), kóvar (OR 2,5) eða hjartmagnýl og kóvar samtímis (OR 30,7). Enginn af ALGIB sjúklingum þurfti á skurðaðgerð að halda og tíðni dauðsfalla var mjög lág (1,2%). Nýgengi obscure GIB var 10 tilfelli *per* 100.000 íbúa á ári. Sjúklingar með óústkýrða sýnilega GIB voru líklegri en viðmiðunarhópur til þess að nota NSAID (OR 2,0) og kóvar (OR 3,9). Slíkt hið sama gilti um sjúklinga með óútskýrða leynda GIB, OR 2,0 fyrir NSAID og 4,5 fyrir kóvar. Einungis 1,6% sjúklinga með óútskýrða leynda GIB greindust með krabbamein í ristli eftir þriggja ára eftirfylgd. Af sjúklingum með óútskýrða sýnilega GIB, blæddu 5% aftur á tímabili eftirfylgdar sem var minnst þrjú ár, af sjúklingum með óútskýrða leynda blæðingu blæddu 6% aftur og 3,5% af viðmiðum. Það var ekki tölfræðilega marktækur munur á tíðni annarrar blæðingar milli hópa. Í heildina voru 74% þeirra sem greindust með ristil- eða endaþarmskrabbamein með blæðingartengd einkenni, af þeim voru 61% með sýnilega blæðingu. Þeir sem voru með blæðingartengd einkenni voru ólíklegri en þeir án blæðingartengdra einkenna til þess að vera með meinvörp við greiningu (OR 0,56). Þeir sem voru með sýnilega blæðingu voru líklegri til þess að vera á kóvar miðað við þá án blæðingartengdra einkenna (OR 3,2). Það var ekki munur á notkun hjartamagnýl á milli blæðara og þeirra án blæðingartengdra einkenna.

Bráðar blæðingar frá meltingarvegi eru algengar en nýgengi blæðinga sem ekki finnst orsök fyrir eftir hefðbundna uppvinnslu er lágt. NSAID, hjartamagnýl og kóvar virðast eiga stóran þátt í blæðingum frá meltingarvegi og þessi lyf auka hættu á klínískt marktækri blæðingu. Skammtímahorfur sjúklinga með bráða blæðingu eru góðar og hið sama gildir um langtímahorfur sjúklinga með óútskýrða blæðingu frá meltingarvegi. Sjúklingar með blæðingartengd einkenni frá ristil- eða endaþarmskrabbameini greinast fyrr en þeir án þeirra. Kóvar kann að auka líkur á því að sjúklingar fái blæðingartengd einkenni.

Lykilorð: Blæðingar frá meltingarvegi, bólgueyðandi lyf sem ekki eru sterar, hjartamagnýl, warfarin.

Abstract

Gastrointestinal bleeding (GIB) is a common reason for hospitalization and referral to endoscopy. Certain drugs seem to be associated with GIB, although their role in specific types of GIB and etiology is unclear. The outcome of patients with GIB seems to be favourable although long-term follow-up data is lacking.

The aim of this thesis was to evaluate the incidence of gastrointestinal bleeding as well as to describe its etiology. Furthermore, to study the association of GIB and various drugs potentially associated with GIB and to determine the short- and long-term outcome in GIB patients. Lastly, to examine what proportion of patients with colorectal cancer have bleeding-related symptoms and what characterizes those patients.

The total cohort of the thesis included all patients that underwent endoscopy at the National University Hospital of Iceland in 2010 and all of those who underwent colonoscopy in 2013 at the National University Hospital of Iceland. The indications and results of endoscopies were prospectively noted. Endoscopic nurses interviewed patients on drug history prior to endoscopy. Furthermore, drug history was obtained by reviewing medical records and by access to a nationwide pharmaceutical database. Patients were further divided to 4 main cohorts: patients with acute upper gastrointestinal bleeding (AUGIB) in 2010, patients with acute lower gastrointestinal bleeding (ALGIB) in 2010, patients with ALGIB in both 2010 and 2013 and lastly, patients with unexplained GIB in 2010. Patients with unexplained bleeding were further categorized to patients with: unexplained overt GIB, unexplained occult GIB, obscure GIB and clinical suspicion of bleeding. Unexplained bleeders were retrospectively followed-up for at least three years. Controls were selected from patients undergoing endoscopy in the same period and matched for gender and age (±5 years). In addition, all patients diagnosed with colorectal cancer in Iceland from 2008-2011 were identified *via* the Icelandic Cancer Registry and their medical records retrospectively reviewed with respect to bleeding-related symptoms.

The most common etiologies of AUGIB were peptic ulcer (40%), Mallory-Weiss tears (12%) and oesophagitis (10%). The incidence of AUGIB was 87/100,000 inhabitants *per* year in the greater metropolitan area of Reykjavik, increasing with age. The following drugs were associated with AUGIB, non-steroidal anti-inflammatory drugs (NSAIDs) (p = 0.0002), low-dose aspirin (LDA) (p = 0.0371) and warfarin (p = 0.0069). NSAID use was associated with clinically significant AUGIB (Odds ratio – OR 6.6). The need for acute surgery in AUGIB was low (1.9%) and the rate of AUGIB-related deaths was very low

(1.3%). The most common etiologies of ALGIB were diverticulosis (23%), ischemic colitis (16%) and inflammatory-bowel disease (12%). The incidence for ALGIB was also 87/100,000 inhabitants *per* year in the greater metropolitan area of Reykjavik, increasing with age. The use of NSAIDs, LDA and warfarin as well as concomitant use of LDA and warfarin was associated with ALGIB, odds ratio (OR) 3.5, 1.5, 2.8 and 3.6, respectively. Furthermore, bleeding from diverticulosis was associated with NSAIDs (OR 8.8), LDA (OR 2.0) and warfarin (OR 2.7). Ischemic colitis was associated with LDA (OR 2.3) and IBD with NSAIDs (OR 3.4). Patients with clinically significant ALGIB were more likely than bleeders without clinically significant bleeding to be using NSAIDs, warfarin and combined therapy of LDA and warfarin, OR 2.0, 2.5 and 30.7, respectively. No patient underwent acute surgery for ALGIB and the rate of ALGIB-related deaths was very low (1.2%). Of patients with unexplained bleeding, the incidence of obscure GIB was 10/100,000 inhabitants *per* year. The use of NSAIDs or warfarin was associated with both unexplained overt GIB and unexplained occult GIB, OR 2.0 and OR 2.0 for NSAID use, respectively, OR 3.9 and OR 4.5 for warfarin use, respectively. Only 1.6% of patients with unexplained occult bleeding were diagnosed with new/missed colorectal cancer in a mean follow-up of 3.0 years. Patients with unexplained overt and unexplained occult GIB were not more likely than controls to have another bleeding episode during a follow-up of at least three years, 5%, 6% and 3.5% respectively. Of patients diagnosed with colorectal cancer, 74% had bleeding-related symptoms, of those 61% had overt symptoms. Patients with bleeding-related symptoms were less likely than non-bleeders to have metastases at diagnosis (OR 0.56). Warfarin was associated with overt bleeding symptoms when compared to controls, OR 3.2. However, LDA use was not associated with bleeding-related symptoms.

Acute gastrointestinal bleeding is common, while obscure GIB is rare. The use of NSAIDs, LDA and warfarin seem to play an important role in gastrointestinal bleeding throughout the gastrointestinal tract and may increase risk of clinically significant bleeding. The short-term outcome of patients with acute GIB is generally good and the long-term outcome of patients with unexplained GIB is favourable. Colorectal cancer patients with bleeding-related symptoms present earlier than nonbleeders. Warfarin may increase the odds of bleeding-related symptoms, resulting in a earlier diagnosis.

Keywords: Gastrointestinal bleeding, non-steroidal anti-inflammatory drugs, low-dose aspirin, warfarin.

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List of abbreviations

AUGIB…….Acute upper gastrointestinal bleeding

ALGIB…….Acute lower gastrointestinal bleeding

CE……Capsule endoscopy

CRC…….....Colorectal cancer

DBE…….Double-balloon enteroscopy

EBL…….Endoscopic band ligation

EGD……Esophagogastroduodenoscopy

FOBT……...Faecal occult blood test

GIB …….Gastrointestinal bleeding

Hb……Haemoglobin

IBD……..Inflammatory-bowel disease

ICR…….....……...Icelandic Cancer Registry

IDA……..Iron deficiency anemia

IMA…….Icelandic Medicine Agency

IMR…….The Icelandic Medicines Registry

INR……..International Normalized Ratio

LDA…….Low-dose aspirin

LMWH……Low-molecular-weight heparin

MCV……Mean corpuscular volume

NSAID…….Non-steroidal anti-inflammatory drugs

PT……Prothrombin time

PU……Peptic ulcer

RBC…….Red blood cell

SSRI……Selective serotonin reuptake inhibitors

TRBC……..Technetium 99m-labeled red blood cell

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List of papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-IV) as needed:

I. Hreinsson, J. P., Kalaitzakis, E., Guðmundsson, S., Björnsson, E. S. (2013). Upper gastrointestinal bleeding: incidence, etiology and outcomes in a population-based setting. *Scandinavian Journal of Gastroenterology, 48*(4), 439-447.

II. Hreinsson, J. P., Guðmundsson, S., Kalaitzakis, E., Björnsson, E. S. (2013). Lower gastrointestinal bleeding: incidence, etiology, and outcomes in a population-based setting. *European Journal of Gastroenterology & Hepatology*, *25*(1), 37-43.

III. Hreinsson, J. P., Pálsdóttir, S., Björnsson, E.S. (2014). The association of drugs with severity and specific causes of acute lower gastrointestinal bleeding: a prospective study. *[Manuscript]*.

IV. Hreinsson, J. P., Bjarnason, I., Björnsson, E.S. (2014). The outcome and role of drugs in patients with unexplained gastrointestinal bleeding. *[Manuscript]*.

V. Hreinsson, J. P., Jónasson, J. G., Björnsson, E.S. (2014). Bleeding-related symptoms in colorectal cancer: a 4-year nationwide population-based study. *Alimentary Pharmacology & Therapeutics*, *39*(1), 77-84.

Declaration of contribution

I, Jóhann Páll Hreinsson, declare that I participated in all of the papers presented in this thesis. My contribution was as follows:

Paper I – Data collection, statistical analysis, writing of manuscript and participating in its revision.

Paper II – Data collection, statistical analysis, writing of manuscript and participating in its revision.

Paper III – Study design, data collection, statistical analysis, writing of manuscript and participating in its revision.

Paper IV – Study design, data collection, statistical analysis, writing of manuscript and participating in its revision.

Paper V – Study design, data collection, statistical analysis, writing of manuscript and participating in its revision.

1. Introduction

Gastrointestinal bleeding (GIB) affects a significant proportion of the population in various forms. Traditionally, acute GIB is defined as gastrointestinal bleeding leading to hospitalization or occurring in a hospitalized patient (Arroja et al., 2011; Blatchford et al., 1997; Longstreth, 1997; Rockall et al., 1995) and is further categorized to upper and lower GIB. Upper and lower GIB is divided by the ligament of Treitz, which is situated at the junction between the duodenum and jejunum (Arroja et al., 2011; Lanas et al., 2009; Longstreth, 1997; Makela et al., 1993). Recently, the definition of mid-GIB has been proposed (Ell & May, 2006; Raju et al., 2007), which would only include bleeding from the small intestine. Technically, bleeding from the small intestine is now a part of lower GIB. The presentation of GIB can be overt, occult or obscure. Overt bleeding presents with haematemesis, rectal bleeding or melaena whereas occult GIB presents with iron deficiency anemia (IDA) and/or a positive faecal occult blood test (FOBT). Obscure bleeding can present both in an overt and occult manner (Raju et al., 2007).

1.1. Acute upper gastrointestinal bleeding

The reported incidence of acute upper gastrointestinal bleeding (AUGIB) spans a wide range of 36-172 *per* 100,000 inhabitants and year (Ahsberg et al., 2010; Blatchford et al., 1997; Button et al., 2011; Czernichow et al., 2000; Lanas et al., 2009; Longstreth, 1995; Loperfido et al., 2009; Paspatis et al., 2012; Paspatis et al., 2000; Rockall et al., 1995; Theocharis et al., 2008; Thomopoulos et al., 2004; van Leerdam et al., 2003; Yavorski et al., 1995). Before the turn of the century AUGIB was a serious event that often led to surgery and even death (Blatchford et al., 1997; Loperfido et al., 2009; Rockall et al., 1995). H_2 receptor antagonists, that could heal peptic ulcer (PU), emerged in the 1970's (Pearlman, 1976) and later, the proton pump inhibitors (PPIs) in the late 1980's (Vanderhoff & Tahboub, 2002). In the second part of last century, scientific understanding of the role of *h. pylori* was evolving (Marshall & Warren, 1984) and non-steroidal anti-inflammatory drugs (NSAIDs) have also had a great impact on AUGIB treatment strategy. Improvement in pharmacological treatment of PU and prophylactic PPI therapy have probably led to a decrease in the

incidence and mortality of AUGIB in recent decades (Lanas et al., 2009; Loperfido et al., 2009; van Leerdam et al., 2003).

1.1.1. Causes of peptic ulcer

There are two known factors that are strongly associated with PU, that can in some instances lead to AUGIB. These factors are the bacterium *helicobacter pylori (h. pylori)* and NSAIDs.

Helicobacter pylori and its role in the pathogenesis of PU was discovered by the Australian doctors, Barry Marshall and Robin Warren (Marshall & Warren, 1984). The precise mechanism by which *h. pylori* causes PU is not known (Kusters et al., 2006). However, there are some factors that are likely to play a vital role. The bacterium produces urease which protects the bacterium from the acidity of the stomach and can cause cellular damage as well (Nilius & Malfertheiner, 1996). *H. pylori* produces lipase which can damage gastric cell membranes (Nilius & Malfertheiner, 1996) and the mucosal coating of the stomach (Slomiany et al., 1989). The bacterium has been shown to have an inhibitory effect on somatostatin secretion, resulting in a decrease in the inhibition of gastrin secretion (an acid secretion stimulator) (Queiroz et al., 1993).

NSAIDs are a class of drugs that are widely used to reduce inflammation, pain response and fever. Their mode of action involves inhibition of the enzyme cyclo-oxygenase (COX) which transforms arachidonic acid to prostaglandines (Vane, 1971). The COX enzyme has two significant isoforms. Firstly, the COX-1 which is associated with maintaining integrity of the gastric mucosa, normal renal function and platelet aggregation, secondly, the COX-2 that contributes to inflammatory pain (Flower, 2003). Furthermore, NSAIDs have been shown to have a topical effect on the gastric mucosa (Bjarnason, 2013), mainly by two mechanisms. Firstly, they have adverse effects on both the mucous gel layer covering the gastric mucosa *via* interactions with phospholipids, as well as the surface of gastric cell membranes, and thereby causing damage to the gastric mucosa (Lichtenberger, 2001). Secondly, intracellular build-up occurs during absorption of NSAIDs which disrupts intracellular pathways and intercellular junctions by affecting mitochondrial oxidative

phosphorylation (Somasundaram et al., 1997). The combination of these topical effects and the systemic effects of COX-1 inhibition can lead to PU (Bjarnason, 2013).

1.1.2. Etiology

The most common cause of AUGIB is peptic ulcer disease (Table 1). The prevalence of other causes such as oesophagitis, Mallory-Weiss tears, erosions and gastroduodenitis varies greatly between studies, which might be explained by a discrepancy in methodology (Table 1). Upper GI neoplasms and varices are reported to range from 2-8% and 6-12%, respectively (Table 1). Angiodysplasia remain an uncommon cause of AUGIB (Table 1). Other uncommon causes include Zollinger-Ellison syndrome, portal hypertensive gastropathy, anastomotic ulcers and Dieulafoy's lesion (Lee & Laberge, 2004).

	Blatchford et al. (1997) *n (%)*	van Leerdam et al. (2003) *n (%)*	Theocharis et al. (2008) *n (%)*	Loperfido et al. (2009) *n (%)*	Range
No. of patients	1882	769	353	539	353-1882
Etiology					
Peptic ulcer	520 (28)	350 (46)	237 (67)	286 (53)	28-67%
Gastric ulcer	201 (11)	128 (17)	113 (32)	91 (17)	11-32%
Duodenal ulcer	319 (17)	222 (29)	116 (33)	179 (33)	17-33%
Oesophagitis	330 (18)	---	---	23 (4)	4-18%
Mallory-Weiss	125 (7)	---	15 (4)	16 (3)	3-7%
Gastroduodenal lesions[1]	486 (26)	158 (20)[2]	30 (8)	56 (10)	8-26%
Neoplasm	36 (2)	39 (5)	28 (8)	28 (5)	2-8%
Angiodysplasia	---	---	---	15 (3)	3%
Variceal bleeding	107 (6)	56 (7)	22 (6)	62 (12)	6-12%
No finding	545 (29)	107 (14)	12 (3)	27 (5)	3-29%
Rebleeding rate	---	119 (16)	26 (7)	40 (7)	7-16%
Surgery	---	---	11 (3)	11 (2)	2-3%
Mortality rate	153 (8)	102 (13)	10 (4)	49 (9)	4-13%

[1]Erosions, gastroduodenitis [2]Includes oesophagitis, Mallory-Weiss, erosions, gastroduodenitis

Table 1. *Etiology and outcome of acute upper gastrointestinal bleeding in several studies*.

1.1.3. Outcome

The rebleeding rate of patients treated for AUGIB is around 7-16% (Table 1). PU and oesophageal varices are responsible for 70% of rebleeding instances (van Leerdam et al., 2003). A recent meta-analysis showed the rebleeding rates of non-variceal AUGIB to be 7% and 13% after hemostasis by endoscopic clips or thermocoagulation (± adrenalin injection), respectively (Sung et al., 2007). Recent reports indicate that approximately 2-3% of patients with AUGIB require surgery (Table 1). One study comparing surgical rates in bleeders in 1986-7 vs. 2000-1 showed a reduction from 14% to 5.3% (Thomopoulos et al., 2004). The mortality of AUGIB has been reported to be 4-13% (Table 1). This rate is confounded by the fact that some studies report all-cause mortality, while others do not. The mortality rate directly related to AUGIB is likely to be low (Loperfido et al., 2009; Peura et al., 1997).

1.2. Lower gastrointestinal bleeding

The incidence of acute lower gastrointestinal bleeding (ALGIB) has been reported to be 21-43/100,000 inhabitants *per* year in three retrospective studies (Ahsberg et al., 2010; Lanas et al., 2009; Longstreth, 1997). Furthermore, the incidence of ALGIB has been reported to be increasing whereas the incidence of AUGIB is decreasing (Lanas et al., 2009).

1.2.1. Etiology

The most common cause of ALGIB is diverticulosis in most studies, ranging from 15-42% in different studies (Table 2). It is important to keep in mind that diverticular bleeding is often a presumptive diagnosis since active bleeding from diverticula is rarely witnessed (Wong Kee Song & Baron, 2008). Other common causes include ischemic colitis, colon cancer and hemorrhoids (Table 2). Inflammatory bowel disease (IBD) and bleeding from polyps have a proportion of 3-7% and 5-9%, respectively (Table 2). Angiodysplasia and post-polypectomy bleeding are uncommon causes of ALGIB (Table 2).

	Makela et al. (1993) *n (%)*	Longstreth (1997) *n (%)*	Gayer et al. (2009) *n (%)*	Arroja et al. (2011) *n (%)*	Range
No. of patients	266	219	608	364	
Diverticulosis	39 (15)	91 (42)	227 (34)	77 (21)	15-42%
Ischemic colitis	-	19 (9)	65 (11)	88 (24)	9-24%
Colon cancer	20 (8)	20 (9)	72 (12)[1]	46 (12)	8-12%
IBD	17 (6)	16 (7)	33 (5)	11 (3)	3-7%
Hemorrhoids	56 (21)	10 (5)	128 (21)	14 (4)	4-21%
Postpolypectomy	-	9 (4)	-	14 (4)	4%
No finding	63 (31)	26 (12)	21 (3)	30 (8)	3-31%
Angiodysplasia	13 (5)	6 (3)	14 (2)	18 (5)	2-5%
Colonic polyps	23 (9)	-	-	18 (5)	5-9%
Endoscopic therapy	8 (3)	7 (3)	24 (4)	80 (22)	3-22%
Emergency surgery	29 (11)	7 (3)	29 (4)	5 (1.4)	3-11%
Mortality related to bleeding	11 (4)	1 (0.5)	-	0%	0-4%

[1]Categorized as neoplasia

Table 2. *Etiology and outcome of acute lower gastrointestinal bleeding in several studies.*

1.2.2. Outcome

The prognosis for patients with ALGIB is generally good. Endoscopic therapy is mainly used to treat angiodysplasia, for removing polyps and to handle post-polypectomy bleeding (Farrell & Friedman, 2005). Bleeding from diverticulosis is also possible to treat endoscopically (Pilichos & Bobotis, 2008). Emergency surgery is rare for patients with ALGIB (Table 2). ALGIB usually resolves without surgery and it is generally recommended that surgery should be reserved for patients with hemodynamic instability despite aggressive resuscitation, patients with a blood transfusion requirement of more than six red blood cell units or severe rebleeding (Farrell & Friedman, 2005). The mortality rate of patients with ALGIB is very low, the reported rate of deaths directly related to bleeding is 0-4% (Table 2).

1.3. Treatment of gastrointestinal bleeding

GIB can be treated with pharmaceuticals, endoscopic therapy and surgery.

The main type of drugs used in the treatment of AUGIB are proton pump inhibitors (PPIs). PPIs lower the acidity in the stomach and have been shown to be effective in treating oesophagitis as well as peptic ulcers and erosive lesions (Shi & Klotz, 2008), which account for the majority of AUGIB (Table 1). In PU disease, PPIs reduce the risk of rebleeding and the need for repeated endoscopic treatment (Sung et al., 2009) and they seem to lower the need for surgery as well (Leontiadis et al., 2007). Causes of ALGIB that can be, to some extent, handled pharmaceutically are hemorrhoids and IBD.

Endoscopic treatment can be categorized to injection, ablative and mechanical therapy (Cappell, 2010).

Injection therapy – The most common injection therapy used to achieve hemostasis is injection with epinephrine. Patients with peptic ulcers have a rebleeding rate of 18% when monotherapy with epinephrine is used (Calvet et al., 2004). The rebleeding rate can be lowered to 11% when a second endoscopic treatment (*i.e.* ablative therapy) is added to the monotherapy (Calvet et al., 2004).

Sclerosants are chemicals that cause oedema and acute inflammation in tissue resulting in hemostasis, followed by necrosis and fibrosis (Loperfido et al., 1990). The disadvantages of sclerosants are that they can induce inflammation already present in a tissue as well as causing ulcers at the injection site (Rajgopal et al., 1992). Sclerosants, not costly and easy to use, are mainly used for treating oesophageal varices (Cordon et al., 2012). However, they are second choice after rubber band ligation therapy, as the rate of complications is high for sclerotherapy (Cordon et al., 2012). Less commonly used chemicals for injection treatment include thrombin, fibrin glue and cyanoacrylates, none of which is as affective as adrenaline, although thrombin and cyanoacrylates are useful for treating gastric varices (Cappell, 2010).

Ablative therapy – The mechanism of action of ablative therapy involves a medium of heat energy (*i.e.* electricity, heat, argon plasma) aimed at a bleeding site *via* an endoscopic probe, causing coagulation of tissue proteins, oedema and vasoconstriction (Jensen, D. M. & Machiado, G.A., 2005). Ablation therapy is

commonly used as a second treatment after injection therapy, which has been shown to decrease the rate of rebleeding in patients with peptic ulcer (Calvet et al., 2004). Ablative therapy is the main treatment of angiodysplasia. One prospective study showed that the 2-year rebleeding rate for angiodyplasia treated with ablative therapy was 10% and the rate of complications was very low, occurring in only two patients out of 100 patients (Olmos et al., 2006). The patients presented with post-procedural fever and pneumoperitoneum without laparoscopic evidence of perforation, respectively (Olmos et al., 2006).

Mechanical therapy – Mechanical devices can be attached to the end of an endoscope in order to treat various causes of GIB. These devices include, hemoclips, endoscopic band ligation and snares (Cappell, 2010).

Hemoclips are used to stop arterial bleeding, two clips are placed on either side of a bleeding artery resulting in hemostasis (Jensen, D. M., Machiado, G.A & Hirabayashi, K., 2005). If hemoclips are properly placed they can be very affective; when combined with injection therapy the rates of definitive hemostasis, rebleeding and need for surgery have been reported to be 89%, 8% and 1.3%, respectively (Sung et al., 2007). Optimally, the hemoclips come loose in 10-14 days when tissue has healed (Chan et al., 2008). If they come loose sooner it usually occurs during the placement of another hemoclip or during the first 24 hours (Chan et al., 2008). The use of hemoclips generally does not cause complications (Cappell, 2010).

Endoscopic band ligation (EBL) is most commonly used in the treatment of oesophageal varices. A part of an oesophageal varix is suctioned into the endoscope, a rubber band is then placed at the base of the suctioned area resulting in an ischemic polyp-like structure which causes necrosis in the tissue, which then falls off (Cappell, 2010). EBL is most useful as a prophylactic therapy of bleeding from varices, obliterating 92% of varices treated (Khuroo et al., 2005), although it can also be used to treat active bleeding (Laine & Cook, 1995). EBL has been used to treat internal hemorrhoids with good results, 90% of patients are symptom-free for the first two years after treatment (Komborozos et al., 2000). EBL has also been used to treat peptic ulcers and Mallory-Weiss tears (Cappell, 2010).

Snares are used in the removal of polyps. A snare is threaded over a polyp, then tightened until the polyp detaches from the mucosa. Detachable snares are an

alternative to traditional snares, they are only tightened until the polyp becomes ischemic and falls of, similar to variceal treatment with EBL (Rengen & Adler, 2006). The main complications of polypectomy are postpolypectomy bleeding and perforation, with a reported prevalence of 0.5% and 0.03%, respectively (Ko et al., 2010).

Hemospray – An exciting new treatment for GIB has recently emerged. In short, hemostatic powder is sprayed onto a bleeding lesion in order to achieve hemostasis. Preliminary studies are promising, reporting a 95% (Smith et al., 2012) and 100% (Holster et al., 2014) hemostasis rate for AUGIB and ALGIB, respectively. However, no controlled studies have been undertaken so far.

1.4. Occult and obscure gastrointestinal bleeding

The definition of occult and obscure gastrointestinal bleeding varies in the literature, and the line between the two entities is thin. Occult GI bleeding has been defined as bleeding from the gastrointestinal tract that is unknown to the patient who presents with IDA and/or a positive FOBT (Rockey, 2010; Zuckerman et al., 2000). The American Gastroenterological Association (AGA) has defined obscure gastrointestinal bleeding (OGIB) as "a bleeding of unknown origin that persists or recurs (*i.e.*, recurrent or persistent IDA, FOBT positivity or visible bleeding) after a negative initial or primary endoscopy (colonoscopy and/or upper endoscopy) result" (Zuckerman et al., 2000). More recently, the AGA have added negative radiological evaluation (such as small bowel follow-through or enteroclysis) to the definition (Raju et al., 2007). Furthermore, OGIB is often categorized to overt and occult obscure gastrointestinal bleeding (Raju et al., 2007). Although the causes of obscure GIB and effectiveness of diagnostic modalities have been studied, the incidence of obscure GIB is unknown.

1.4.1. Occult gastrointestinal bleeding

Iron deficiency anemia is a common medical problem. The prevalence of IDA in the USA is thought to be 2-3% in men older than 16 years and 6-9% in women 50 and older, higher in menstruating women (Looker et al., 2002). The incidence figures of IDA are not available in the general population. IDA is thought to be caused by gastrointestinal blood loss in the majority of patients with IDA, when excluding premenopausal women (Zuckerman et al., 2000). However, there is a lack of data on the proportion of IDA caused by GIB in the general population as studies investigating this, focus on GI causes and for the most part, only include patients with IDA referred to an gastroenterological evaluation (Bampton & Holloway, 1996; Kepczyk & Kadakia, 1995; Rockey & Cello, 1993; Stray & Weberg, 2006). In studies investigating patients suspected of occult GIB a potential bleeding source is found in 50-84% of patients (Table 3). Causes of IDA besides GIB include menstruation, Coeliac's disease, gastrectomy, *h. pylori* colonization and blood donation (Goddard et al., 2011).

1.4.1.1. Etiology

Several studies have examined the etiology of occult GI bleeding (Table 3). Although the results of these studies vary greatly, the most common potential source of occult bleeding in the upper gastrointestinal tract seems to be oesophagitis and gastritis, followed by peptic ulcer. However, angiodysplasia, malignancy and Coeliac's disease remain rather uncommon causes (Table 3). Colorectal cancer and polyps in the colon are common causes of occult GI bleeding in the large intestine, while angiodysplasia and inflammatory bowel disease have been found to be relatively uncommon causes of bleeding (Table 3). Other uncommon causes include Cameron's lesion (Cameron & Higgins, 1986) and anastomotic ulcers (Rockey & Cello, 1993).

A likely cause of the varying results are major differences in study design. In some of the studies patients were required to have IDA, with or without a positive FOBT and *vice versa*, in one study a positive FOBT or an IDA diagnosis was sufficient to be included (Table 3). All of the studies had clear, similar predetermined criteria for lesions that could potentially cause occult GI bleeding, except for Hardwick and Armstrong (Table 3).

	Zuckerman and Benitez (1992) n (%)	*Rockey and Cello (1993) n (%)*	*Kepczyk and Kadakia (1995) n (%)*	*Bampton and Holloway (1996) n (%)*	*Hardwick and Armstrong (1997) n (%)*	*Stray and Weberg (2006) n (%)*	*% range*
Patient characteristics	Positive FOBT ± IDA	IDA ± positive FOBT	IDA ± positive FOBT	IDA ± positive FOBT	IDA	IDA and/or FOBT	
Number of patients	100	100	70	80	89	219	70-219
Potential bleeding source found	53(53)	62 (62)	50 (71)	49 (61)	75 (84)	110 (50)	50-84%
Upper GI source	36 (36)	37 (37)	39 (56)	38 (48)	51 (57)	48 (22)	22-57%
Oesophagitis	6 (6)	6 (6)	10 (14)	14 (18)	26 (29)	3 (1)	1-29%
Gastric ulcer	6 (6)	5 (5)	3 (4)	3 (4)	10 (11)	12 (6)	4-11%
Duodenal ulcer	1 (1)	11 (11)	3 (4)	5 (6)		3 (1)	1-11%
Malignancy	---	1 (1)	3 (4)	1 (1)	12 (14)	2 (1)	1-4%
Angiodysplasia	8 (8)	3 (3)	4 (6)	2 (3)		5 (2)	2-8%
Gastritis	12 (12)	6 (6)	11 (16)	2 (3)		5 (2)	2-16%
Coeliac's disease	---	---	4 (6)	0 (0)	2 (2)	8 (4)	2-4%
Colorectal source	26 (26)	26 (26)	21 (30)	16 (20)	50 (56)	87 (40)	20-56%
Colorectal cancer	6 (6)	11 (11)	4 (6)	7 (9)	31 (35)	36 (16)	6-35%
Polyps	14 (14)	5 (5)	7 (10)	5 (6)	8 (9)	41 (19)	5-19%
Angiodysplasia	5 (5)	5 (5)	6 (9)	1 (1)	2 (2)	7 (3)	1-9%
Colitis	---	2 (2)	---	1 (1)	8 (9)	3 (1)	1-9%

Table 3. *Prospective studies examining the potential causes of occult GI bleeding.*

1.4.1.2. Treatment

The most important aspect in the management of patients with IDA is to identify the etiology of IDA prior to initiation of therapy. Thereafter, the treatment of occult GI bleeding can be either by compensating for blood and iron loss *via* blood transfusion or iron supplementation. Specific etiologies of IDA, such as polyps or angiodysplasia, can be treated directly with an endoscopic device. Other examples (*i.e.* colorectal cancer) can be treated with surgery.

Administration of oral iron supplement is usually the first line of treatment for IDA (Goddard et al., 2011) and therefore, occult GIB as well. After oral iron therapy is initiated the amount of reticulocytes in blood should increase in 3-7 days, followed by an increase in red blood cells (Alleyne et al., 2008). If oral iron therapy is not sufficient to reverse the anemia, it is likely explained by either that the loss of iron in the gastrointestinal tract cannot be compensated for by the amount of iron the GI tract absorbed in a given time, or by patient non-compliance. Although iron supplementation is relatively safe, gastrointestinal discomfort is thought to occur in 10-20% of patients receiving oral iron (Rimon et al., 2005). Apparent inability of oral iron therapy to treat GI blood loss, patient non-compliance and intolerance for oral iron, are an indication for parenteral iron therapy, usually administered intravenously (Johnson-Wimbley & Graham, 2011). The increase in hemoglobin by intravenous iron therapy has been shown to be similar to oral therapy after 12 weeks of treatment (Breymann et al., 2008). The advantage of intravenous therapy is that it raises transferrin saturation and ferritin levels, indicating that it replenishes iron stores which oral therapy does not (Breymann et al., 2008). The prevalence of anaphylaxis during intravenous iron therapy has been reported to be from 0.002-0.7% (Silverstein & Rodgers, 2004).

Chronic occult GIB can cause severe anemia that may require blood transfusion. Blood transfusion is indicated when a patient has symptomatic anemia or is at risk for cardiovascular instability because of severe anemia (Goddard et al., 2011). Blood transfusion swiftly alleviates anemic symptoms such as dyspnea, dizziness and fatigue. However, although complications of blood transfusion (*i.e.* ABO-incompatible blood transfusion, transfusion-related acute lung injury and viral

infections) are rare, they can have serious consequences for the patient and even lead to death (Goodnough, 2005).

Further treatment, such as endoscopic measures or surgery are discussed in chapter 1.3, treatment of gastrointestinal bleeding and chapter 1.1.2.3, treatment of obscure GIB.

1.4.1.3. Outcome

In patients suspected of occult GI bleeding, bidirectional endoscopy reveals a potential bleeding source in 50-84% of the cases (Table 3) and the outcome of these patients depends on the etiology of bleeding. Occult GIB caused by colon carcinoma is removed surgically in the majority of cases and after successful radical surgery, there is no risk of re-bleeding. Another example is oesophagitis which is effectively treated with proton pump inhibitors (Donnellan et al., 2005). However the patient could develop occult GIB from oesophagitis again after PPI cessation. The rebleeding rate of angiodysplasia has been reported to be 30-56% (Hayat et al., 2000; Landi et al., 2002; Lin et al., 2009).

For patients with idiopathic IDA, there are indications that iron supplementation is the best first line treatment and is in many cases sufficient. One study, analyzing IDA patients without gastrointestinal symptoms, showed that of 29 patients that were followed for a median of 24 months, only one patient had recurrent anemia whereas all the other patients responded to iron supplementation (Wilcox et al., 1997a). A prospective study showed that of 38 patients with idiopathic IDA, 30 (83%) no longer had anemia when seen in follow-up, with a mean of 20 months (Rockey & Cello, 1993). One patient was later diagnosed with gastritis and the remaining seven were either lost to follow-up or had serious medical illnesses (Rockey & Cello, 1993). A study following 69 patient (mean age 68 years) with IDA and a negative bidirectional endoscopy for a mean of 39 months, showed that the IDA resolved in 49 (71%) of the patients (Gordon et al., 1996). In only 5 (7%) of the remaining 20 patients the anemia was unresolved and in other 15 the anemia was likely to be explained by other medical illnesses (Gordon et al., 1996). The most recent study investigating idiopathic IDA after GI evaluation was a retrospective long-term follow-up study reporting data from 1997-2000 (McLoughlin & Tham,

2009). The study showed that after 5.8 years of follow-up, anemia resolved in 83% of 57 patients (McLoughlin & Tham, 2009).

It is conceivable that some patients with idiopathic IDA will be diagnosed with a missed malignancy later on. However, in the four studies mentioned above, only two patients were diagnosed with colon cancer during follow-up (McLoughlin & Tham, 2009; Wilcox et al., 1997a) and one of these patients had an incomplete index colonoscopy (Wilcox et al., 1997a). A new/missed cancer after colonoscopy is defined as a diagnosis made after the patient has previously undergone a colonoscopy 6-36 months prior to cancer diagnosis (Bressler et al., 2007; Singh et al., 2010). One study examining the new/miss rate for proximal colon cancer, which is more prone to cause IDA than distal cancer, showed that of 4920 patients diagnosed with proximal cancer, 4% had a colonoscopy 6-36 months prior to diagnosis (Bressler et al., 2004). Two large population-based studies showed that the rate of new/missed colorectal cancer in the general population was 3.4% (Bressler et al., 2007) and 7.9% (Singh et al., 2010). Two prospective studies determining the rate of missed lesion with back-to-back colonoscopies revealed that the miss rate for adenomas ≥1 cm in 183 patients (Rex et al., 1997) and 294 patients (Heresbach et al., 2008) was 6% and 9%, respectively. None of the 9/183 and 4/294 cancers diagnosed were missed (Heresbach et al., 2008; Rex et al., 1997).

1.4.2. Obscure gastrointestinal bleeding

Of patients with clinically evident bleeding, approximately 5% remain undiagnosed despite routine investigations (Rockey, 2010). There has been a rapid progress in the diagnosis and treatment of these patients in the last two decades with the introduction of capsule endoscopy and advances in endoscopic technology. The incidence of obscure GIB is, to our knowledge, unknown and there have been no longitudinal or population-based studies performed to explore that question.

1.4.2.1. Etiology

The causes of obscure GIB can be categorized into the four classes displayed in Table 4. Vascular lesions seem to be the most common cause of obscure GIB originating in the small intestine, whereas neoplasia and erosions/ulcers seem to be less common (Table 4). The focus for obscure GIB cannot be located, in as many as one half of patients (Table 4).

	Mehdizadeh et al. (2006)	Ohmiya et al. (2007)	Arakawa et al. (2009)	Marmo et al. (2009)	Range
Number of patients	130	479	162	193	130-479
Type of study	Prospective	Prospective	Retrospective	Prospective	
Diagnosis	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
Small-bowel bleeding	130 (51)	226 (47)	95 (59)	132 (68)	47-68%
Vascular lesions/diseases	42 (32)	66 (14)	37 (23)	72 (37)	14-37%
Tumors and polyps	10 (8)	54 (11)	21 (13)	30 (16)	8-16%
Ulcerations and erosions	11 (8)	86 (18)	27 (17)	12 (6)	6-18%
Meckel's diverticulum	---	9 (2)	7 (4)	---	2-4%
Upper GI bleeding	---	26 (5)	4 (3)	---	3-5%
Lower GI bleeding	---	25 (5)	11 (7)	---	5-7%
Normal or non-definite finding	64 (49)	202 (42)	52 (32)	61 (32)	32-49%

Table 4. *Etiology of obscure GIB. N/S: Not specified.*

Vascular lesions or diseases can include angiodysplasia (the most common type), Dieulafoy's lesion, small-bowel ulcers associated with allergic purpura and ischemic enteritis (Arakawa et al., 2009; Ohmiya et al., 2007). Ulcers and erosions can include NSAID enteropathy, Behcet's disease, simple ulcer, intestinal tuberculosis, Crohn's disease, peptic ulcer, amyloidosis and radiation injury (Arakawa et al., 2009; Ohmiya et al., 2007). Other uncommon causes are Coeliac's disease, hemobilia, and aortoenteric fistula (Raju et al., 2007). Bleeding from the upper GI tract and the colorectum seems to be responsible for around 10% of obscure GIB (Arakawa et al., 2009; Ohmiya et al., 2007). The causes for obscure bleeding outside of the small intestine have been reported to be duodenal ulcer, varices, colonic diverticulosis and carcinoma (Arakawa et al., 2009). Other causes may include Cameron's lesion, gastric ulcer, gastric antral vascular ectasia (GAVE) and angiodysplasia (Raju et al., 2007). Some causes of obscure GIB originating in the small intestine are age-dependent: angiodysplasia and NSAID enteropathy are more common in patients older than 40 years of age, while tumors, Crohn's disease, Dieulafoy's lesion and Meckel's diverticulum are more common in patients 39 years old and younger (Raju et al., 2007).

1.4.2.2. Diagnosis

There are several options available in the diagnosis of obscure GIB. The diagnostic approaches available are endoscopic, radiological and surgical measures. As suggested in a recent review paper on occult and obscure GIB the first analytical approach depends on the severity of the bleeding (Rockey, 2010). Patients with aggressive or massive bleeding should undergo angiography and/or red blood cell (RBC) scintigraphy, or be considered for surgical intervention (Rockey, 2010). For patients with less severe bleeding, repeat endoscopy should be undertaken in most cases but this decision should be based on the clinical symptoms. Otherwise the patient should undergo capsular endoscopy, enteroscopy or other diagnostic studies (Rockey, 2010).

Radiographic studies appropriate for the diagnosis of obscure GIB include, angiography, nuclear studies (RBC scintigraphy, Meckel's scan), barium studies

(enteroclysis and small bowel follow-through), computed tomography and magnetic resonance imaging.

Mesenteric angiography should be considered for active bleeders. This technique is dependent on the severity of the bleeding and is capable of locating the site of bleeding when the rate of bleeding is at least ≥0.5 mL/min (720 mL/24 hours) (Zuckerman et al., 2000). A review article analyzing 14 studies found the yield of angiography to be 27-77% (Zuckerman & Prakash, 1998). However, the range becomes narrower when only patients with active bleeding are studied, or 61-72% (Browder et al., 1986; Ng et al., 1997). Provocative angiography (inducing bleeding with medication) has been suggested to increase the yield of angiography. This method is controversial since it could, in theory, result in uncontrollable bleeding. However, one study of seven patients undergoing provocative angiography found the procedure to be safe in these patients (Bloomfeld et al., 2000). However, only two out of seven (30%) patients were diagnosed with a source of bleeding, suggesting that provocation of bleeding does not increase diagnostic yield (Bloomfeld et al., 2000).

RBC scintigraphy is a convenient method for diagnosing GIB, especially when preceding angiography. The most common type of scintigraphy is the technetium 99m-labeled red blood cell (TRBC) scan. The TRBC scan is not as invasive as angiography and more sensitive since it detects a bleeding rate of 0.1-0.4 mL/min (144-576 mL/24 hours) (Alavi et al., 1977; Rantis et al., 1995; Smith et al., 1987). Two retrospective studies on obscure GIB found the proportion of positive TRBC scans to be 39% (excluding upper GIB) (Olds et al., 2005) and 36% (Tabibian et al., 2013). Of those patients, 48% and 41% were subsequently diagnosed with a cause of bleeding, respectively. This suggests that the diagnostic yield of TRBC scans for obscure GIB is poor.

Barium studies such as small bowel follow-through and enteroclysis are useful when it comes to diagnosing Crohn's disease or irregularities in the GI tract such as tumors, however, their ability to discern mucosal lesion is very poor (Diner et al., 1984). Likewise, the diagnostic yield of these studies has been shown to be very low in the diagnosis of obscure GIB, or around 6% (Triester et al., 2005). The role of these studies seems to be decreasing with the advancement of capsule endoscopy and enteroscopy.

There are four main endoscopic techniques used in the diagnosis of obscure GIB: push enteroscopy, deep enteroscopy (includes single- double-balloon and spiral enteroscopy), capsule endoscopy (CE) and intraoperative enteroscopy (Fisher et al., 2010). Other techniques include sonde enteroscopy (Sidhu et al., 2008). CE has been shown to have a higher diagnostic yield than push enteroscopy and radiographic techniques (Raju et al., 2007). A meta-analysis comparing the diagnostic yield of CE vs. push enteroscopy and CE vs. small-bowel barium studies, showed the difference to be 63% vs. 28% and 42% vs. 6%, respectively (Triester et al., 2005). In the comparison of CE and double-balloon enteroscopy (DBE), the studies show conflicting results. One meta-analysis demonstrated that when pooling five studies with a total cohort of 219, CE had a higher diagnostic yield in diagnosing obscure GIB than DBE (total diagnostic yield = 63% vs. 50%, OR 1.67, CI 1.44-2.44) (Chen et al., 2007). Another meta-analysis comparing the diagnostic yield of CE and DBE in 375 patients with small-bowel diseases (350 of which had obscure GIB) there was no difference between CE and DBE, or 60% vs. 57%, respectively (Pasha et al., 2008). However, as many have suggested, rather than choosing either one, CE and DBE should be used to complement each other usually starting with CE since it is more convenient (Table 5) (Raju et al., 2007; Rockey, 2010; Sidhu et al., 2008).

CE		**DBE**		**Intraoperative endoscopy**	
Advantages	*Disadvantages*	*Advantages*	*Disadvantages*	*Advantages*	*Disadvantages*
No sedation or anesthesia	No ability to treat	Ability to treat	Requires sedation or anesthesia	Highest diagnostic yield	Risk of mortality
Non-invasive	Risk of retention	Safe	Invasive	Ability to treat	Risk of complications
Readings not confounded by trauma	Only displays images, irregularities cannot be examined beyond that		Can cause trauma confounding readings		Can cause trauma confounding readings

Table 5. *Advantages and disadvantages of the main modalities for diagnosing obscure GIB.*

Intra-operative endoscopy is usually regarded as the gold standard in diagnosing obscure GIB and has been reported to have a diagnostic yield of 70-88% (Raju et al., 2007). Although effective, the rate of recurrent bleeding after intraoperative endoscopy is 13-60% and mortality ranges from 0-17% (Raju et al., 2007). Furthermore, the risk of complications is higher than for the other procedures and therefore it is recommended as a last resort for massive bleeders (Raju et al., 2007; Sidhu et al., 2008).

1.4.2.3. Treatment

The discontinuation of NSAIDs and LDA is recommended for obscure bleeders in the same way as for acute upper and lower gastrointestinal bleeders (Rockey, 2010). Some obscure bleeders require iron supplemental therapy or blood transfusions as discussed in chapter 1.1.1.2. The same applies to causes for obscure GIB treatable with an endoscopic device or by surgery as described in chapter 1.3.

Endoscopic treatment for obscure GIB mainly includes cauterization of angiodysplasia, although there is a scarcity of data on cauterizations of small intestinal angiodysplasia. In one study, a total of 55 patients with small intestinal angiodysplasia underwent cauterization (Askin & Lewis, 1996). The mean red blood cell units transfused per month before intervention was 2.40 ± 2.97, and 0.32 ± 0.91 after cauterization ($p < 0.0001$) (Askin & Lewis, 1996). Another study showed similar results, transfusion need lowered from 13 ± 6 to 6 ± 3 per year and 4/13 (31%) patients no longer required transfusions (Vakil et al., 1997).

Regarding pharmacological therapies, there have been some reports of drug efficacy but randomized controlled trials are lacking. A small observational study reported that hormonal therapy was effective in preventing rebleeding in obscure GI bleeders (Barkin & Ross, 1998), 38 patients received combination hormonal therapy and none of them rebled as long as they continued therapy, mean follow-up 535 days (25 of the patients had angiodysplasia, no source was located in the remaining 18). In contrast, a double-blind, randomized placebo-controlled trial studying the efficacy of hormonal therapy in preventing rebleeding from angiodysplasia showed no difference in rebleeding rate among those receiving treatment vs. placebo, 39% and 46%, respectively (Junquera et al., 2001). A recent review investigating the use of

somatostatin analogues in the treatment of angiodysplasia showed that in a total of three studies involving 62 patients, blood transfusion requirement lowered by 2.2 (CI 3.9-0.5) after treatment (Brown et al., 2010). Other small studies have shown that octreotide may be helpful in preventing rebleeding from angiodysplasia (Junquera et al., 2007; Nardone et al., 1999).

1.4.2.4. Outcome

There are three main subjects of interest in the outcome of obscure GI bleeders; resolution of bleeding, risk of rebleeding and mortality.

In a well-performed follow-up study, 91 patients with obscure GIB who underwent capsule endoscopy, 59 (65%) had resolution of bleeding during a mean follow-up time of 18 months (range 5-25 months) (Pennazio et al., 2004). Furthermore, the cohort was categorized into obscure-occult, previous obscure-overt and ongoing obscure-overt, the proportion of resolved bleeding in these groups was 69%, 41% and 87%, respectively (Pennazio et al., 2004). A similar study reported resolution of obscure GIB for 72% of 95 patients, 85% in overt and 53% in occult obscure bleeders (Estevez et al., 2006). The rebleeding rate of obscure GIB has been reported to be 17-30% (Fujimori et al., 2007; Landi et al., 2002; Lin et al., 2009). The rebleeding rate of angiodysplasia has been found to be 30-56% (Hayat et al., 2000; Landi et al., 2002; Lin et al., 2009).

Death caused by obscure GIB is extremely rare, with various studies reporting a mortality rate of zero or not reporting on mortality (Estevez et al., 2006; Lin et al., 2009; Pennazio et al., 2004).

1.5. Drugs and gastrointestinal bleeding

Drugs play an important role in gastrointestinal bleeding. Non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin (LDA) and warfarin are all drugs that have been associated with gastrointestinal bleeding (Delaney et al., 2007; Lanas et al., 2011; Sostres et al., 2013). LDA is a type of NSAID, however, it is often classified individually apart from other NSAIDs. Although aspirin, at higher doses, has anti-inflammatory effects by inhibiting COX-2 function like other NSAIDs (Simmons et al., 2004), it is primarily a COX-1 blocker as the sensitivity of COX-2 in regards to aspirin is 10- to 100-fold lower than COX-1 (Simmons et al., 2004) and at low doses the COX-2 inhibition is minimal. Furthermore, aspirin blocks platelet function irreversibly (*via* COX-1) (Loll et al., 1995), unlike other NSAIDs that have reversible effects on platelet function (Ouellet et al., 2001).

1.5.1. Drugs and AUGIB

The association of AUGIB and NSAIDs is well established (Carson et al., 1987; Gabriel et al., 1991; Hernandez-Diaz & Rodriguez, 2000; Sostres et al., 2010). The use of NSAIDs may increase the odds of a bleeding peptic ulcer four- to fivefold overall, twofold for ibuprofen users and fourfold for diclofenac users (Langman et al., 1994). In studies investigating risk factors for severe AUGIB, NSAID use has either not been noted (Blatchford et al., 2000) or has not been a predictive factor for severe bleeding (Corley et al., 1998; Marmo et al., 2008; Rockall et al., 1996).

The use of LDA has also been shown to be associated with AUGIB (Garcia Rodriguez et al., 2011; Hallas et al., 2006; Sorensen et al., 2000). There is a scarcity of data concerning the incidence of AUGIB among LDA users outside of clinical trials. One population-based study examined the incidence of AUGIB among patients placed on LDA after being discharged from a cardiology department, thus not including primary prevention users (Serrano et al., 2002). The incidence of AUGIB during 3.8 years of follow-up was 1.2 *per* 100 patient-years (Serrano et al., 2002).

Most studies investigating the association of warfarin and AUGIB are performed in a clinical setting and/or report any GIB rather than focusing on site of bleeding. There is a scarcity of data regarding the association of warfarin and AUGIB in the general population. One population-based study in Denmark showed warfarin

to be associated with AUGIB (Hallas et al., 2006). In a randomized controlled trial studying the efficacy and safety of LDA and warfarin (Hurlen et al., 2002), 2% (24/1206) of LDA users vs. 4% warfarin users (48/1216) had a GIB event ($p = 0.052$). This indicates that the risk of GIB is at least as high in warfarin users as in LDA users. There is a lack of studies investigating the incidence of AUGIB among warfarin users.

1.5.2. Drugs and ALGIB

It has been shown that NSAIDs do not only increase the risk of AUGIB but ALGIB as well (Chang et al., 2011; Holt et al., 1993; Lanas et al., 1992; Langman et al., 1985; Wilcox et al., 1997b). However, many of the studies indicating this association do not distinguish between aspirin and non-aspirin NSAIDs (Holt et al., 1993; Lanas et al., 1992; Langman et al., 1985). A recent retrospective, nationwide study in Taiwan, using ICD-9 codes for case finding, found patients with lower gastrointestinal bleeding to have greater odds than controls to use NSAIDs, OR 2.26 (CI 1.78-2.85) (Chang et al., 2011).

The scientific data for the association of LDA and ALGIB are scarce. Studies have shown that use of LDA is common among lower GI bleeders or 40% (Ahsberg et al., 2010) and 35% (defined as anti-aggregants) (Arroja et al., 2011). Two large prospective cohort studies, recently compared patients using aspirin ≥6 a week and nonusers (Huang et al., 2010, 2011). Aspirin users were more likely to have ALGIB both in men, OR 1.34 (CI 1.00–1.79) (Huang et al., 2010), and women OR 1.55 (CI 1.15-2.09) (Huang et al., 2011). However, these studies, among other studies reporting aspirin to be associated with ALGIB (Holt et al., 1993; Lanas et al., 1992; Langman et al., 1985), did not differentiate between regular, and low-dose aspirin.

Data on the role of warfarin in ALGIB are limited in the same manner as in AUGIB as previously mentioned. Studies have mainly shown an association of warfarin and any GIB (Delaney et al., 2007; Hurlen et al., 2002).

A nationwide study in Spain showed that NSAIDs and LDA may be attributed in as many as 36% of ALGIB-related deaths (Lanas et al., 2005). This may indicate that NSAIDs and LDA are associated with more severe bleeding. Some studies have found NSAID use does not predict outcome (Strate et al., 2003; Wilcox & Clark, 1997). In contrast, LDA has been associated with clinically significant ALGIB (Lanas

et al., 2005; Strate et al., 2003). The concomitant use of LDA and warfarin seems to increase the odds of ALGIB in comparison to monotherapy (Delaney et al., 2007; Hansen et al., 2010; Lanas et al., 2011). There is a lack of studies investigating the risk of clinically significant bleeding among all bleeders on warfarin.

In terms of drugs and specific etiologies of ALGIB, NSAIDs and LDA seem to have a role in diverticular bleeding (Kvasnovsky et al., 2013; Strate et al., 2011; Yuhara et al., 2013), whereas there is a lack of data on the association of warfarin and diverticular bleeding. NSAIDs have been proposed to cause flares in IBD, although data on this association remain inconclusive (Feagins & Cryer, 2010). Ischemic colitis is a common cause of ALGIB (Table 2), and has been shown to be associated with LDA (Fernandez et al., 2010). However, studies investigating the association of drugs and ALGIB caused by ischemic colitis are lacking.

1.5.3. Drugs and occult & obscure gastrointestinal bleeding

NSAIDs have convincingly been shown to have an adverse effect on the small intestinal mucosa (NSAID enteropathy) (Adebayo & Bjarnason, 2006). In 40 volunteers taking 75mg of slow-release diclofenac twice a day for two weeks, 68% had new mucosal lesions recognized on capsule endoscopy (Maiden et al., 2005). Arakawa *et al.* demonstrated that of 162 obscure bleeders 11% were NSAID users and 5/162 (3.1%) of bleeders had NSAID enteropathy recognized as a cause of obscure GI bleeding (Arakawa et al., 2009). Another study showed that NSAIDs were the cause of obscure GIB in 3.6% (17/479) of cases (Ohmiya et al., 2007). Despite this data, there is a lack of controlled studies examining this association.

Recent studies indicate that LDA might cause mucosal lesions in the small intestine (Endo et al., 2009; Leung et al., 2007; Smecuol et al., 2009). In a small study comparing 10 healthy individuals on LDA therapy for two weeks with controls receiving no drug, 80% of LDA users had small-bowel pathology vs. 20% of controls (Endo et al., 2009). In a similar study of 20 healthy individuals using LDA for two weeks and acting as own controls, 50% were shown to have mucosal damage on capsule endoscopy (Smecuol et al., 2009). A study of 22 LDA users undergoing capsule endoscopy (obscure GIB being the indication for 21/22) revealed that 64%

(14/22) of the patients had mucosal damage (Endo et al., 2009). This association requires further research.

NSAID use among patients with occult GI bleeding seems to be common. Studies have reported prevalence of NSAID use among occult GI bleeders to be from 11-60% (Bampton & Holloway, 1996; Kepczyk & Kadakia, 1995; Rockey & Cello, 1993). The use of NSAIDs or LDA was 22% (Stray & Weberg, 2006) and 33% (Zuckerman & Benitez, 1992) in two studies not discerning between the two drugs. A systematic review of studies measuring faecal occult blood loss *via* radioactively labeled autologous erythrocytes demonstrated that patients using LDA and ibuprofen had a weighted mean blood loss of 1.6 and 2 mL/day, respectively, higher than the patient baseline of 0.46 mL/day (Moore et al., 2008). Prospective controlled studies examining the role of NSAIDs and LDA in occult GIB are limited.

There is also a scarcity of data on the role of other anticoagulants, such as warfarin, in obscure and occult gastrointestinal bleeding.

1.5.4. Drugs and colorectal cancer

Both NSAIDs and LDA have been shown to have a protective effect against colorectal cancer (CRC) (Din et al., 2010; Rothwell et al., 2010). The anti-inflammatory effects of NSAIDs might reduce the chance of cancer forming since chronic inflammation has been associated with cancers (Coussens & Werb, 2002). It could be expected that the effect of NSAIDs and LDA on the gastrointestinal mucosa might increase the odds of tumors starting to bleed, which might result in an earlier diagnosis of CRC. However, there is a lack of studies examining if NSAIDs or LDA are associated with bleeding from CRC.

Warfarin may induce bleeding from neoplasia possibly causing an earlier detection of the disease (Asiimwe et al., 2013; Johannsdottir et al., 2012; Kershenbaum et al., 2010). One study demonstrated that when comparing FOBT positive patients on warfarin with patients not on warfarin in a population-based setting, diagnosis of clinically significant adenomas was more common in patients on warfarin vs. non-users (8.9/1000 vs. 4.0/1000) (Kershenbaum et al., 2010). A study following the complete blood count of 3218 patients on warfarin led to the detection of 14 precancerous lesions and 10 colorectal cancers (Johannsdottir et al., 2012).

1.6. Colorectal cancer and gastrointestinal bleeding

In the Nordic countries, CRC is the most common non-gender specific cancer (Engholm G, 2013). The age-standardized rate in the Nordic countries is 35.4 and 27.3 for males and females, respectively, and CRC is responsible for a little over 12% of all cancer deaths (Engholm G, 2013). The incidence of CRC has been increasing in recent decades, in contrast, the age-standardized rate for mortality has been decreasing (Engholm G, 2013).

1.6.1. Presentation of colorectal cancer

The presenting symptoms and signs of CRC may be divided into bleeding-related symptoms and nonbleeding-related symptoms (symptoms and signs will be referred to as symptoms for convenience). Bleeding-related symptoms include both occult bleeding, presenting with IDA or/and a positive faecal occult blood test, and overt bleeding, presenting with rectal bleeding or melaena. The most common presenting symptoms of CRC are anemia (57-60%), abdominal pain (44-64%), changes in bowel habits (42-65%) and rectal bleeding (37-58%) (Alexiusdottir et al., 2012; Cappell, 2008; Korsgaard et al., 2006; Majumdar et al., 1999). Other symptoms of note are weight loss, fatigue, tenesmus (*i.e.* feeling of incomplete defecation) and mucus in stools (Alexiusdottir et al., 2012; Korsgaard et al., 2006). Although both rectal bleeding and anemia have been reported to be common there is a lack of studies that distinguish between overt and occult bleeding. Furthermore, "anemia" in studies usually includes both acute anemia and chronic anemia that results in IDA.

Recent studies show that the rate of obstructive symptoms among CRC patients seem to be present at diagnosis in 4-14% of cases (Benedix et al., 2010; Jullumstro et al., 2009; Majumdar et al., 1999).

1.6.2. Proximal versus distal cancer

Proximal cancer (right-sided cancer) is usually defined as cancer in the colon proximal to the splenic flexure (Gonzalez et al., 2001). It varies between studies whether distal cancer is defined as cancer from the splenic flexure to the rectum or including the rectum. The proportion of proximal cancer compared to distal cancer has been increasing in recent decades (Jessup et al., 1996), this is thought to stem

from more colonic polyps being detected and removed in the distal colon (Cress et al., 2000).

The presentation of proximal and distal cancers varies in regard to symptoms. Patients with proximal cancer are more likely to present with anemia (Alexiusdottir et al., 2012; Majumdar et al., 1999), whilst distal cancer is more likely to present with rectal bleeding, change in bowel habits and tenesmus (Alexiusdottir et al., 2012; Majumdar et al., 1999).

Proximal cancers have been associated with poorer differentiation of CRC (Benedix et al., 2010; Nawa et al., 2008; Snaebjornsson et al., 2010) as well as a more advanced stage (Benedix et al., 2010; Meguid et al., 2008; Nawa et al., 2008; Snaebjornsson et al., 2010) indicating that proximal cancer generally presents at a later stage in the course of the disease, which might suggest that distal cancer symptoms prompt earlier diagnostic work-up.

2. Aims

The general aims of the studies described in this thesis were to study gastrointestinal bleeding in a population-based setting. Specific aims were as follows:

1. To evaluate the incidence, etiology and outcome of AUGIB in a population-based setting, analyse the role of drugs in AUGIB and find independent predictors of clinically significant bleeding (Paper I).

2. To evaluate the incidence, etiology and outcome of ALGIB in a population-based setting, analyse the role of drugs in ALGIB and find independent predictors of clinically significant bleeding (Paper II)

3. To study the potential association of drugs and specific causes of ALGIB. Furthermore, to identify drugs associated with clinically significant ALGIB (Paper III).

4. To study patients with unexplained gastrointestinal bleeding, further categorized to unexplained overt, occult and obscure bleeding. In order to determine the outcome of these patients with a three-year follow-up and to study the association of drugs and these patients. Lastly, to ascertain the incidence of obscure GIB (Paper IV).

5. To examine what proportion of patients diagnosed with colorectal cancer have bleeding-related symptoms in a nationwide setting, study what defines these bleeders and to find independent predictors of having bleeding-related symptoms (Paper V).

3. Material and methods

3.1. Setting and case finding

The overall cohort of the study may be divided into three separate cohorts.

Cohort I – Consisted of all patients undergoing esophagogastroduodenoscopy (EGD) and/or colonoscopy in the National University Hospital of Iceland in the year 2010 (*Papers I-IV*). This was a prospectively registered, population-based cohort.

Cohort II – Consisted of all patients undergoing colonoscopy in the National University Hospital of Iceland in the year 2013 (*Paper III*). This was a prospectively registered, population-based cohort.

Cohort III – Consisted of all of those diagnosed with colorectal cancer in Iceland from 2008-2011 (*Paper V*). Data were provided by the Icelandic Cancer Registry (ICR). The ICR is a nationwide cancer registry which has been shown to have a completeness of over 99% (Sigurdardottir et al., 2012). Data in this nationwide cohort were obtained retrospectively.

3.2. Data collection and variables

In *Papers I-IV*, indications and results of endoscopies were recorded in a prospective manner by the operating gastroenterologists. The specialist noted whether or not GI bleeding was present or suspected and if the bleeding was considered clinically significant.

Drug history was obtained by endoscopic nurses before the endoscopic procedure and the use of the following drugs was recorded: NSAIDs, LDA, warfarin, platelet inhibitors, LMWH/heparin, SSRIs, bisphosphonates[1], corticosteroids and PPIs. The patient drug use had to be on a continuous basis. NSAID users were defined as patients who used NSAIDs daily for a minimum of 5 days. To improve the drug history of patients, their medical records were reviewed and the Icelandic Medicines Registry (IMR) was accessed. Data from the IMR on prescriptions issued for patients from January 1st 2009 to December 31st 2010 in *Papers I-IV*, and additionally, from January 1st 2012 to December 31st 2013 for *Paper III* were obtained. The IMR is run

[1] Not recorded in cohort II

by the Directorate of Health in Iceland and registers all prescriptions issued outside of hospitals and nursing homes in Iceland. It contains data from 2002 and onward, about 2,300,000 registrations are added to the database annually.

Laboratory values collected from medical charts were: Hb (g/l), mean corpuscular volume (fL), haematocrit (%), platelet counts, creatinine (mmol/l), prothrombin time (PT, s), the International Normalized Ratio (INR), serum iron (μmol/L), total iron-binding capacity (μmol/L) and serum ferritin (μg/L).

In *Papers I* and *II*, data on blood transfusions were provided by the Blood Bank of Reykjavík, which provides blood products to the National University Hospital. All information on transfusions is stored in an electronic information system (Prosang, Databyran, Sweden) and full traceability is ensured.

In *Paper I*, information from the Icelandic Medicine Agency (IMA) was used to calculate the incidence of AUGIB among LDA and warfarin users. The IMA is a governmental agency under the Ministry of Health and Social Securities. IMA holds information on the total amount of every individual drug sold by every wholesaler to every pharmacy, nursing home and hospital in Iceland. Information on the use or sale of prescribed drugs in these institutions was also accessible. The IMA provided information on the amount of LDA sold by wholesalers in the greater metropolitan area of Reykjavík in 2010. Warfarin is only available by prescription and therefore the IMA was able to provide data on how many individuals were treated with warfarin in hospitals, nursing homes or had a prescription for warfarin.

All studies were approved by the Bioethics Committee of Iceland and the Data Protection Authority of Iceland.

3.3. Inclusion and exclusion criteria

Paper I – Data on patients with AUGIB in *Cohort I* were analyzed and compared to controls. AUGIB was defined as:

1) Haematemesis or coffee ground vomiting along with presentation to the emergency room, hospitalization of patient, or occurring in a hospitalized patient.
2) Melaena along with hospitalization or occurring in a hospitalized patient.
3) Rectal bleeding with a confirmed cause of bleeding on EGD and a negative colonoscopy along with hospitalization or occurring in a hospitalized patient.

Of all the patients that underwent EGD, the following were excluded:

(1) Individuals undergoing EGD for other reasons than UGIB or suspicion of UGIB.
(2) Patients suspected of occult bleeding because of anemia, iron-deficiency anemia and/or a positive FOBT with no diagnosis on endoscopy.
(3) Patients with melena and no signs of bleeding revealed in EGD and colonoscopy.
(4) Individuals who had overt GIB but were not hospitalized.
(5) Patients with occult bleeding and a confirmed cause of bleeding.

Paper II –Patients with acute lower gastrointestinal bleeding (ALGIB) were the focus of this study and were also selected from *Cohort I*. ALGIB was defined as:

(1) Passage of bright red blood *per* rectum or maroon-colored stool without haematemesis leading to hospitalization or occurring in a hospitalized patient.
(2) Melaena with a confirmed cause of bleeding on colonoscopy and a negative EGD along with hospitalization or occurring in a hospitalized patient.

Of all the patients that underwent colonoscopy, the following were excluded:

(1) Individuals undergoing colonoscopy for reasons other than LGIB or a suspicion of LGIB.
(2) Patients suspected of occult bleeding because of anemia, iron deficiency anemia, and/or a positive FOBT with no diagnosis at endoscopy.
(3) Patients with melaena and no signs of bleeding in EGD and colonoscopy.
(4) Individuals who had overt GI bleeding but were not hospitalized.
(5) Patients with occult bleeding and a confirmed cause of bleeding.

Paper III – Inclusion criteria for *Paper III* were the same as in *Paper II*.
Individuals from *Cohort I* and *II* were pooled together and patients with ALGIB were selected from the cohort. The definition for ALGIB was the same as in *Paper II*.

Paper IV – The following inclusion criteria were set for *Paper IV*:

1) *Unexplained overt GIB* – Patients that had overt upper or lower GI bleeding that did not persist or recur with a negative upper and/or lower endoscopy. All patients during the 2010 prospective study who were referred to endoscopy by a general physician or presented to the emergency room, became after that ambulant, were hospitalized and/or occurred in already hospitalized patients, were included.

2) *Unexplained occult GIB* - Patients with IDA and/or a positive FOBT, the anemia not persisting or recurring. Patients with suspicion of other causes for IDA than gastrointestinal blood loss, such as anemia of chronic diseases, excessive menstruation, extreme nutritional deficiencies or gastric surgery, were excluded.

3) *Obscure GIB* - Patients with obvious persisting or recurrent bleeding and no source of bleeding after bidirectional endoscopy. If patients did not have signs of bleeding after bidirectional endoscopy they were excluded. Patients that underwent further diagnostic work-up, such as capsule endoscopy or red blood cell scan, were included regardless of further signs of bleeding after bidirectional endoscopy.

    a. *Overt obscure GIB* – Patients with overt signs of bleeding, haematemesis, rectal bleeding and melaena.

    b. *Occult obscure GIB* - Patients with recurrent or persistent IDA requiring iron supplementation and/or blood transfusion on two separate occasions or more often were included. Patients suspected to have other causes for IDA than GI blood loss were excluded.

4) *High clinical suspicion of bleeding* - Defined as a drop of ≥20 g/L in hemoglobin in two weeks or less, without obvious cause such as blood loss associated with surgery or chemotherapy.

5) *Low clinical suspicion of bleeding* - Patients with normocytic anemia without evidence of iron deficiency, as the sole indication for endoscopy.

Paper V – Patients diagnosed with the ICD-10 numbers, C18.0–C18.9 (malignant tumours of the colon) and C19 (malignant tumours of the recto-sigmoid junction) as well as C20 (cancer in rectum) were included and the tumours had to be classified as adenocarcinomas and invade beyond the *muscularis mucosae* to be included. Cancers of the appendix (C18.1) and anal cancers (C21) were excluded.

3.4. Definitions

Clinically significant bleeding (Papers I-III) – Patients needed blood transfusions (hemoglobin (Hb) < 100 g/l), became haemodynamically unstable (pulse > 100, systolic pressure < 100 mm/Hg), were admitted to the intensive care unit, required surgery or died.

Bleeding-related symptoms (Paper V) – Rectal bleeding or melaena (with a negative EGD), IDA or a positive FOBT. Rectal bleeding and melaena were considered to be overt bleeding whereas IDA and a positive FOBT were defined as occult bleeding.

Another bleeding episode (Paper IV) - Defined as evidence of gastrointestinal bleeding more than 30 days after index endoscopy.

New and/or missed cancer diagnosis (Paper IV) - Defined as a diagnosis of cancer after a negative colonoscopy performed 6-36 months after index colonoscopy (Bressler et al., 2007).

Iron deficiency anemia (Paper IV-V) - If anemia was present along with low MCV, low serum iron, high total iron binding capacity or low ferritin, the anemia was considered to be IDA. IDA was also considered to be present if this was noted in medical charts by a gastroenterologist.

Obstructive symptoms (Paper V) - Either a confirmed diagnosis of ileus or subileus; or dilated intestines on x-ray or an appearance on a CT-scan believed to stem from obstruction.

Distal cancer (Paper V) – Defined as cancer in the splenic flexure and beyond, the remaining parts of the colon were defined as proximal cancer.

Accidental diagnosis (Paper V) – Defined as a diagnosis made during work-up for another illness and the diagnosing strategy was not prompted by symptoms or was requested by the patient.

Pathology parameters (Paper V) – Depth of tumour infiltration (T1, T2, T3 and T4), nodal status (N0, N1 and N2), distant metastases (M0 and M1) and tumour stage (TNM-stage) (I, II, III and IV), determined according to the AJCC 6th edition (Greene, 2002). Data on staging for patients with rectal cancers who underwent pre-operative radiation (n = 48) were excluded to prevent treatment bias.

3.5. Controls

Paper I – The controls consisted of those patients in *Cohort I* that underwent EGD in 2010 and were not suspected of, or had GIB. Bleeders and controls were matched 1:2 for gender and age (±5 years).

Paper II-III – The controls consisted of those patients in *Cohort I* and *II* that underwent colonoscopy in 2010 and 2013 and were not suspected of, or had, GIB. Bleeders and controls were matched 1:1 for gender and age (±5 years).

Paper IV – The controls consisted of those patients in *Cohort I* that underwent EGD in 2010 and were not suspected of, or had GIB. Unexplained bleeders and controls were matched 1:1 for gender and age (±5 years).

3.6. Statistics

The statistical chapters from *Papers I-IV* are presented here in the same manner as they were in the *Papers*.

Paper I – All data were processed in Microsoft Office Excel 2010 and IBM SPSS statistics. The chi-square goodness-of-fit test, the Fisher's exact test and the Freeman–Halton test were used to test differences between groups regarding dichotomous variables. Unpaired Mann–Whitney U test and the Kruskal–Wallis test were used to compare continuous variables. Variables with a significant *p*-value in the univariate analysis were entered into a multiple logistic regression analyses in an attempt to identify independent predictors of having an AUGIB and clinically significant bleeding. All tests were two-tailed and were conducted at a 5% significance level. The results are presented as medians and interquartile range (IQR) or means and standard deviation (SD).

Paper II – All data were processed in Microsoft Office Excel 2010 (Microsoft, Redmond, Washington, USA) and IBM SPSS Statistics (IBM, Armonk, New York, USA). The chi-square goodness-of-fit test and the Fisher Exact test were used to test differences between groups regarding dichotomous variables. The unpaired Mann–Whitney U-test was used to compare continuous variables. Variables with a significant *p*-value in the univariate analysis were entered in multiple logistic regression analyses in an attempt to identify independent predictors of having a LGIB and clinically significant bleeding. All tests were two-tailed and were carried out at a 5% significance level. The results are presented as medians and interquartile range or means and SD.

Paper III - All data were processed in Microsoft Office Excel 2010 (Microsoft, Redmond, Washington, USA) and SAS Enterprise Guide 4.3 (SAS Institute Incorporation, Cary, NC, USA). A two-tailed Student's t-test was used to test differences between groups regarding continuous variables. The Fisher Exact test was used to test differences between groups regarding dichotomous variables. Variables thought to be relevant in the multivariate analysis were selected *a priori* and entered into a full fitted model. All tests were two-tailed and carried out at a 5% significance level. All confidence intervals spanned 95%. The results are presented as mean and standard deviation (SD).

Paper IV - All data were processed in Microsoft Office Excel 2010 (Microsoft, Redmond, Washington, USA) and SAS Enterprise Guide 4.3 (SAS Institute Incorporation, Cary, NC, USA). A two-tailed t-test was used to test for differences between groups in continuous variables and the Fisher Exact test was used to test for differences between groups regarding dichotomous variables. Variables selected *a priori* to be included in a multiple logistic regression analyses were: age and the use of NSAIDs, LDA, warfarin and PPIs. A full model fit was used. All tests were two-tailed and were carried out at a 5% significance level. The results are presented as means and standard deviation (SD). All confidence intervals (CI) are 95%.

Paper V – All data were processed using Microsoft Office Excel 2010 (Microsoft, Redmond, WA, USA) and the SAS Enterprise Guide 4.3 (SAS Institute Incorporation, Cary, NC, USA). The chi-squared goodness-of-fit test and the Fisher Exact test were used to test differences between groups regarding dichotomous variables. The unpaired Student's t-test was used to compare continuous variables. Variables found significant at $P < 0.15$ by univariate analysis were subjected to a stepwise logistic regression analysis in an attempt to identify variables independently associated with bleeding-related symptoms. Warfarin use was considered likely to be a confounder and was therefore forced into all the logistic regression models. The results are presented as means and standard deviations (SD). All tests were two-tailed and were carried out at a 5% significance level.

4. Results

4.1. Study cohort

A total of 2471 patients underwent 3335 endoscopies in the year 2010 and 1258 patients underwent 1474 colonoscopies in the year 2013 (Figure 1). The patient cohort investigated in *Paper I* included 156 patients, mean age 66 (±14), with acute upper gastrointestinal bleeding (AUGIB) and 163 patients, mean age 64 (±20), with acute lower gastrointestinal bleeding (ALGIB) in *Paper II* (Figure 1). In *Paper III,* the 163 patients with ALGIB in 2010 and 162 patients with ALGIB in 2013 were pooled together amounting to 325 patients, mean age 64 (±20) (Figure 1). *Paper IV* included 320 patients with unexplained gastrointestinal bleeding, mean age 65 (±18) (Figure 1). They were further categorized into patients with: unexplained overt bleeding, mean age 59 (±18), unexplained occult bleeding, age 68 (±16), obscure GIB, age 67 (±2), high clinical suspicion of GIB, age 69 (±19) and low clinical suspicion of GIB, 71 (±13) (Figure 1). *Paper V* included all patients diagnosed with colorectal cancer in Iceland from 2008-2011, *n = 472,* mean age 69 (±13) (Figure 1). Of those, 348 (74%) patients had bleeding-related symptoms, mean age 69 (±13), further categorized to overt bleeding, age 66 (±13), and occult bleeding, mean age 72 (±12) (Figure 1). There were 124 patients that did not have bleeding-related symptoms, mean age 69 (±13). Thus, the total cohort of this thesis included 4201 patients.

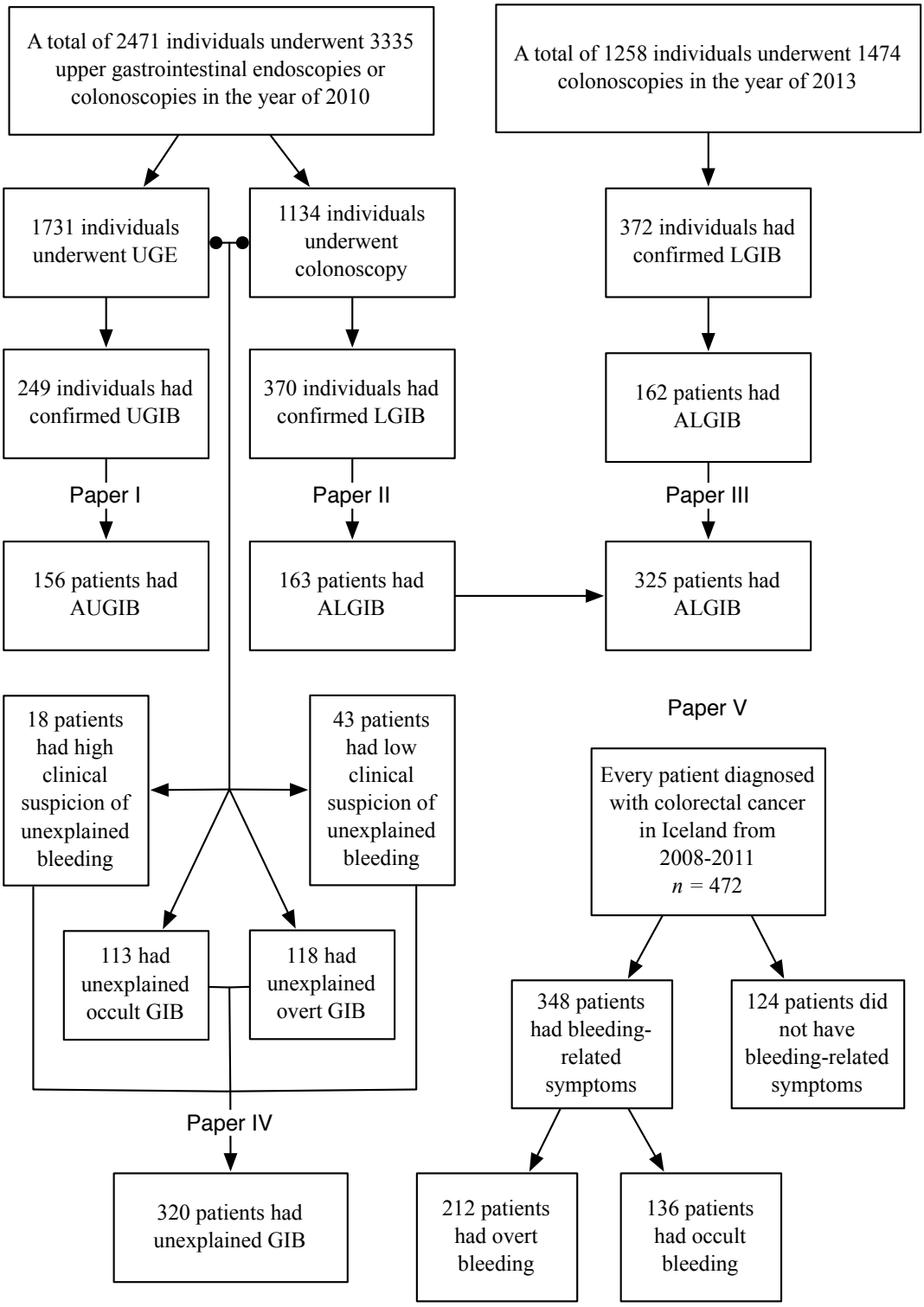

Figure 1. *A flow chart explaining the derivation of patient cohorts.*

4.2. Incidence and etiology of acute and obscure gastrointestinal bleeding

The crude incidence of both acute upper and lower GIB in the greater metropolitan area of Reykjavik was 87/100,000 inhabitants *per* year (Table 6). The incidence of bleeding increased significantly with age in both AUGIB and ALGIB as demonstrated in Table 6. The incidence of obscure gastrointestinal bleeding was 10, 6.5 and 3.5 for obscure, overt obscure and occult obscure GIB, respectively (Table 6). The incidence of overt and occult obscure GIB was lower in patients 39 years old and younger compared to patients of 40 years and older (Table 6).

	AUGIB	**ALGIB**	**Obscure GIB**	**Overt obscure GIB**	**Occult obscure GIB**
Incidence	/100.000	/100.000	/100.000	/100.000	/100.000
Crude incidence rate	87	87	10	6.5	3.5
Age standardized incidence rate					
18-24	30	34	---	---	---
25-39	15	18	---	---	---
<39	---	---	3	3	<1.5*
≥40	---	---	15.5	9.5	6
40-59	48	40	---	---	---
60-79	213	187	---	---	---
80-105	570	690	---	---	---

*There were no patients younger than forty years with occult obscure bleeding in the study period. The incidence 1.5 would represent one patient, thus the incidence is lower than 1.5.

Table 6. *The crude annual incidence and age standardized incidence rates of acute upper and lower GI bleeding, as well as obscure, overt obscure and occult obscure GIB in the greater metropolitan area of Reykjavik. Individuals who were nonresidents of the greater metropolitan area were all excluded.*

The etiologies of AUGIB are displayed in table 7. The most common diagnosis in patients with AUGIB was peptic ulcer disease, or in 41% of patients (Table 7). A greater proportion of patients had duodenal ulcer than gastric ulcer, 21% vs. 15%, respectively, and 5% had both gastric and duodenal ulcer (Table 7). Other common causes of AUGIB were Mallory-Weiss tears and oesophagitis, with a proportion of 12% and 10%, respectively (Table 7). Angiodysplasia, oesophageal varices and gastric cancer were relatively uncommon causes of AUGIB, as only 5%, 4% and 3% of patients had these diagnoses, respectively (Table 7). In 6% of patients a probable cause of AUGIB was not located by endoscopy (Table 7).

The most common endoscopic findings among lower gastrointestinal bleeders were diverticulosis (22%), ischemic colitis (14%), hemorrhoids (12%), and inflammatory-bowel disease in 12% of cases (Table 8). Colorectal cancer was found to be the cause of bleeding in 7% of patients and bleeding was unexplained in 10% of patients with ALGIB (Table 8), similar to the 6% of patients with AUGIB (Table 7). Uncommon causes of ALGIB were angiodysplasia, polyp > 1cm, small intestinal bleeding, anal fissure and post-polypectomy bleeding, with proportions of 1-4% (Table 8).

Diagnosis	*% (n)*
Duodenal ulcer	21 (32)
Gastric ulcer	15 (23)
Mallory-Weiss tear	12 (19)
Oesophagitis	10 (15)
Other	8 (12)
Unexplained bleeding	6 (10)
Angiodysplasia	5 (8)
Gastric and duodenal ulcer	5 (7)
Mucosal erosive disease	5 (7)
Esophageal varices	4 (6)
Ulcer on anastomosis	3 (5)
Gastric cancer	3 (4)
Esophageal ulcer	3 (4)
GIST	3 (4)
Total	156

The diagnoses found in the total study cohort. Among the diagnoses in the group named "Other" were: Three patients had an unknown lesion, and one each of idiopathic thrombocytopenic purpura, portal hypertensive gastropathy, bleeding from the biliary tract caused by cancer invasion, bleeding after a biopsy, bleeding after a papillotomy, herpes esophagitis, bleeding after a partial gastroduodenoectomy, Dieulafoy's lesion, stoma ulcer.
GIST = Gastrointestinal stromal tumor

Table 7. *The etiologies of AUGIB are displayed*

Diagnosis	*% (n)*
Diverticulosis	22 (73)
Ischemic colitis	14 (44)
Hemorrhoids	12 (39)
IBD	12 (38)
Other	11 (35)
Unexplained bleeding	10 (31)
Colorectal cancer	7 (23)
Angiodysplasia	4 (12)
Polyp > 1cm	3 (10)
Small intestinal bleeding	3 (10)
Anal fissure	2 (7)
Postpolypectomy bleeding	1 (3)
Total	325

Among the diagnoses in the group named 'other' were unspecified lesion, NSAID ulcer, Clostridium difficile infection, proctitis, polyp < 1cm, anastomotic ulcer, familial adenamotous polyposis, solitary rectal ulcer, ulcer as a result of cytomegalovirus infection, Escherichia coli infection, jejunal ulcer in a patient with Zollinger–Ellison syndrome, 15cm longitudinal ulcer potentially as a result of constipation, and a case where the bleeding could have been caused by IBD and/or colon cancer.
IBD = Inflammatory bowel disease.

Table 8. *The etiologies of ALGIB are displayed.*

4.3. Role of drugs in gastrointestinal bleeding

4.3.1. Drugs and AUGIB

Patient with AUGIB were more likely than controls to use NSAIDs, 20% vs. 8%, warfarin 15% vs. 7% and LDA, 40% vs. 30% in a univariate analysis (Table 9). Difference in combined therapy with NSAIDs + LDA, LDA + SSRIs and warfarin + SSRIs between bleeders and controls was statistically significant as well (Table 9). Multivariate analysis showed the following drugs to be independently associated with AUGIB; NSAIDs, odds ratio (OR) 2.1 – Confidence interval (CI) 1.1-4.1, warfarin, OR 2.4 (CI 1.3-4.6) and combined use of LDA and SSRIs, OR 2.8 (CI 1.1-7.1) (Table 9). There was not a statistically significant difference between cases and controls in the use of SSRI drugs, platelet inhibitors, bisphosphonates, corticosteroids or LMWH/heparins.

Drug	AUGIB (n = 156)	Control group (n = 312)	*p*-value	OR (CI)
NSAIDs	20% (31)	8% (24)	0.0002	2.1 (1.1-4.1)
NSAIDs + LDA	8% (13)	1% (4)	0.0003	---
Warfarin	15% (23)	7% (21)	0.0069	2.4 (1.3-4.6)
LDA	40% (62)	30% (93)	0.0371	---
LDA + SSRIs	8% (12)	3% (9)	0.0302	2.8 (1.1-7.1)
Warfarin + SSRIs	3% (4)	0% (1)	0.0444	---
PPIs	40% (62)	49% (152)	NS	---

Table 9. *A comparison of drug use among patients with AUGIB compared to controls. All p-values are derived from a univariate analysis, odds ratios and confidences intervals are derived from a multivariate analysis.*

From data provided by the Icelandic Medicines Registry (IMR), it was found that a total of 5,204,600 defined daily doses (DDD) of LDA were sold. By dividing 5,204,600 by 365 it was calculated that 14,259 DDD were used per day. It was assumed that these 14,259 DDD represented the number of individuals using LDA on a regular basis. The number of individuals using LDA (n = 53) in the AUGIB cohort (only including residents in the greater metropolitan area) was then divided by 14,259 resulting in the incidence figure 371/100,000 of AUGIB events among LDA users *per* year in the metropolitan area of Reykjavik.

The same assumptions and calculations were applied in the analysis of AUGIB incidence among warfarin users. The incidence of AUGIB among warfarin users was 1429/100,000 *per* year.

AUGIB patients with and without clinically significant bleeding were 105 and 51, respectively. A greater proportion of clinically significant bleeders were using NSAIDs and NSAID + LDA concomitantly compared to patients without clinically significant bleeding, 27% vs. 6%, p = 0.0023, and 13% vs. 0%, p = 0.0053, respectively. A multivariate analysis revealed NSAID use to be an independent predictor of a clinically significant bleeding. OR 6.6 – CI 1.8–24, p = 0.004.

4.3.2. Drugs and ALGIB

Both *Paper II and Paper III* include data on drug use in patients with ALGIB compared to controls. However, as one of the aims of *Paper III* was to increase the power of analysis with respect to bleeders and controls, mainly data from *Paper III* will be presented here.

In univariate analysis, patients with ALGIB were more likely than controls to use NSAIDs, LDA, warfarin and combination of LDA and warfarin (Table 10). Furthermore, all drugs and combination of drugs were independently associated with ALGIB when correcting for age, gender and use of noted drugs (Table 10). The combinant use of LDA and warfarin had the strongest association with ALGIB, OR 3.6 (CI 1.59-8.3) (Table 10). The lowest OR of the analysis was 1.5 (CI 1.04-2.21) when analysing difference in use of LDA in bleeders and controls (Table 10). Data from *Paper II* revealed patients with ALGIB were more likely to use heparins/LMWHs, 9% vs. 2% ($p = 0.0106$), and there was not a clinically significant difference between bleeders and controls in the use of PPIs, SSRIs, platelet inhibitors, bisphosphonates and corticosteroids.

Drug	**ALGIB** ***(n = 325) - % (n)***	**Controls** ***(n = 325) - % (n)***	***p-value***	**OR (CI)**
NSAID	16 (53)	6 (19)	>0.0001	3.5 (2.00-6.08)
LDA	31 (100)	23 (75)	0.034	1.5 (1.04-2.21)
Warfarin	17 (55)	8 (25)	0.00048	2.8 (1.65-4.69)
LDA + warfarin	7 (24)	2 (8)	0.0057	3.6 (1.59-8.3)

Table 10. *Comparison of patients with ALGIB and controls. All p-values are derived from a univariate analysis and odds ratios and confidences intervals are derived from a multivariate analysis in which age, gender and drugs displayed were corrected for.*

When comparing patients with and without clinically significant ALGIB, a univariate analysis showed the use of NSAIDs, LDA, warfarin and combined use of LDA + warfarin to be associated with clinically significant bleeding (Table 11). In a multivariate analysis the use of both NSAIDs and warfarin was independently associated with clinically significant bleeding (Table 11). However, the use of LDA was not found to be independently associated with clinically significant bleeding (p = 0.1158). The combined use of LDA and warfarin greatly increased the risk of clinically significant bleeding among bleeders, with clinically significant bleeders having the OR of 30.7 (CI 4.07-232), compared to patients without clinically significant bleeding (Table 11).

Drug	**Clinically significant (n = 148) - % (n)**	**Non-clinically significant (n = 177) - % (n)**	***p-value***	**OR (CI)**
NSAID	20 (29)	14 (24)	0.18	2.0 (1.08-3.76)
LDA	39 (57)	24 (43)	0.0078	1.5 (0.90-2.52)
Warfarin	25 (37)	10 (18)	0.00055	2.5 (1.30-4.70)
LDA + warfarin	16 (23)	1 (1)	< 0.0001	30.7 (4.07-232)

Table 11. *Comparison of patients with and without clinically significant bleeding. All p-values are derived from a univariate analysis and odds ratios and confidences intervals are derived from a multivariate analysis in which age, gender and drugs displayed were corrected for.*

Patients with diverticular bleeding had greater odds of drug use than controls both in the uni- and multivariate analysis (Table 12). The strongest relation in the analysis was observed between diverticulosis and the use of NSAIDs, OR 8.8 (CI 4.0-19.2) (Table 12). The use of LDA was associated with bleeding caused by ischemic colitis in the uni- and multivariate analysis (Table 12). Patients with hemorrhoids and IBD were more likely than controls to be on NSAIDs in both the uni- and multivariate analysis (Table 12).

	Use of drug % (*n*)	*p-value*	*OR (CI)*
Diverticulosis (n = 73)			
NSAID	**26 (19)**	**< 0.0001**	**8.8 (4.0-19.2)**
LDA	**43 (31)**	**0.0012**	**2.0 (1.10-3.52)**
Warfarin	**22 (16)**	**0.00096**	**2.7 (1.26-5.59)**
Ischemic colitis (n = 44)			
NSAID	14 (6)	0.0995	2.5 (0.92-6.9)
LDA	**43 (19)**	**0.0088**	**2.3 (1.17-4.56)**
Warfarin	7 (3)	1	0.74 (0.20-2.71)
Hemorrhoids (n = 39)			
NSAID	**21 (8)**	**0.0041**	**4.3 (1.72-10.9)**
LDA	26 (10)	0.69	1.2 (0.51-2.59)
Warfarin	10 (4)	0.54	1.8 (0.56-6.00)
IBD (n = 38)			
NSAID	**18 (7)**	**0.012**	**3.4 (1.17-9.57)**
LDA	**0 (0)**	**0.00017**	---
Warfarin	5 (2)	1	3.7 (0.67-20.5)
Controls (n = 325)			
NSAID	6 (19)	---	---
LDA	23 (75)	---	---
Warfarin	8 (25)	---	---

Table 12. *A comparison of drug use in controls and patients with specific etiology of ALGIB. All p-values are derived from a univariate analysis, all odds ratios and confidences intervals are derived from a multivariate analysis in which age, gender and drugs displayed were corrected for. Statistically significant results are marked in bold typing.*

4.3.3. Drugs and unexplained bleeding

Of all unexplained bleeders, a greater proportion was using warfarin in a univariate analysis (Table 13). Multivariate analysis showed that unexplained bleeders were more likely than controls to use both NSAIDs and warfarin, OR 1.7 and 4.0, respectively (Table 13). The sub-cohorts of patients with unexplained overt and occult GIB were more likely than controls to use both NSAIDs and warfarin in multivariate analysis, OR for overt bleeders 2.0 and 3.9, OR for occult bleeders 2.0 and 4.5, respectively (Table 13). Patients with a low clinical suspicion of bleeding were more likely than controls to use warfarin both in the uni- and multivariate analysis, OR 5.1 (Table 13).

Group	*% (n)*	*p-value*	*OR (CI)*
Unexplained GIB *(n = 320)*			
NSAID	15 (49)	0.057	**1.7 (1.02-2.72)**
LDA	37 (117)	0.16	1.4 (0.97-1.99)
Warfarin	16 (51)	**<0.0001**	**4.0 (2.18-7.39)**
Unexplained overt GIB *(n = 118)*			
NSAID	17 (20)	0.066	**2.0 (1.06-3.79)**
LDA	28 (33)	0.64	1.1 (0.64-1.83)
Warfarin	13 (15)	**0.0052**	**3.9 (1.77-8.67)**
Unexplained occult GIB *(n = 113)*			
NSAID	18 (20)	**0.042**	**2.0 (1.07-3.83)**
LDA	42 (48)	**0.029**	1.5 (0.91-2.41)
Warfarin	19 (22)	**<0.0001**	**4.5 (2.20-9.23)**
Obscure GIB *(n = 28)*			
NSAID	11 (3)	0.75	---
LDA	32 (9)	1.0	---
Warfarin	7 (2)	0.64	---
High clinical suspicion *(n = 18)*			
NSAID	11 (2)	0.70	---
LDA	39 (7)	0.60	---
Warfarin	17 (3)	0.063	---
Low clinical suspicion *(n = 43)*			
NSAID	9 (4)	1.00	1.2 (0.40-3.71)
LDA	47 (20)	0.056	1.7 (0.85-3.48)
Warfarin	21 (9)	**<0.001**	**5.1 (1.96-13.2)**
Controls *(n = 320)*			
NSAID	10 (32)		---
LDA	31 (99)		---
Warfarin	5 (15)		---

Table 13. *A comparison of drug use in patients with unexplained bleeding, their sub-cohorts, and controls. All p-values are derived from a univariate analysis, all odds ratios and confidences intervals are derived from a multivariate analysis in which age, gender, PPI use and drugs displayed were corrected for. Statistically significant results are marked in bold typing.*

4.3.4. Drugs and colorectal cancer

The analysis of drug use among patients diagnosed with colorectal cancer in Iceland from 2008-2011 showed no difference in use of LDA when comparing patients with bleeding-related symptoms to non-bleeders, as well as when comparing overt and occult bleeders to non-bleeders (Table 14). The use of warfarin was more common in both patients with bleeding-related symptoms and overt bleeders when compared to non-bleeders in univariate analysis (Table 14). Overt bleeders had greater odds of warfarin use in multivariate analysis, OR 3.2 (Table 14).

Patient cohort	**Low-dose aspirin**	**Warfarin**
Bleeding-related symptoms (*n* = 348)	24%	9%
Overt bleeders (n = 212)	24%	11%
Occult bleeders (n = 136)	25%	7%
Non-bleeders *(n = 124)*	24%	3%
Univariate analysis		
Bleeders vs. non-bleeders (*p-value)*	NS	<0.05
Overt bleeders vs. Controls (p-value)	---	<0.05
Multivariate analysis		
Bleeders vs. non-bleeders (OR (CI))	---	2.7 (0.94-8.0)
Overt vs. non-bleeders (OR (CI))	---	3.2 (1.04-10.1)
Overt vs. Occult (OR (CI))	---	1.6 (0.63-4.0)
Occult vs. non-bleeders (OR (CI))	---	1.8 (0.53-6.1)

Table 14. *Drug use among patients with colorectal cancer. Variables subjected to a stepwise logistic regression model were age, low-dose aspirin and warfarin use, obstructive symptoms and location of cancer (proximal vs. distal).*

4.4. Outcome of gastrointestinal bleeding

4.4.1. Outcome of AUGIB and ALGIB

The main outcome measures for AUGIB (*Paper I)* and ALGIB *(Paper II)* can be seen in table 15. In all, 67% of AUGIB patients had a clinically significant bleeding, which was more than the 52% of ALGIB patients (Table 15). Of AUGIB patients 60% required blood transfusion and 39% of ALGIB patients (p = 0.0003) (Table 15). Endoscopic treatment was implemented in 24% of AUGIB patients and 7% of ALGIB patients (p < 0.0001) (Table 15). Of AUGIB patients, only 3 (1.9%) required surgery for hemostasis, whereas surgery was not necessary for any patient with ALGIB. Bleeding-related death occurred in 1.3% (n = 2) and 1.2% (n = 2) of patients with AUGIB and ALGIB, respectively (Table 15).

	AUGIB (n = 156)	**ALGIB (n = 163)**	***p-value***
Age	66 (±18.6)	64 (±19.7)	NS
Gender	42% females	50% females	NS
Laboratory values			
Hb	95 (±24.1)	106 (±21.4)	< 0.0001
Haematocrit	0.28 (±0.067)	0.32 (±0.059)	< 0.0001
INR	2.3 (±1.3)	3.1 (±2.2)	NS
Clinically significant bleeding	105 (67%)	84 (52%)	0.0045
Blood transfusion	93 (60%)	64 (39%)	0.0003
Endoscopic treatment	37 (24%)	12 (7%)	< 0.0001
Surgery	3 (1.9%)	0 (0)	NS
Bleeding-related death	2 (1.3%)	2 (1.2%)	NS

Table 15. *A comparison of outcome in acute upper and lower GIB (Data from Paper I and II).*

4.4.2. Outcome of unexplained bleeders

Unexplained overt and occult bleeders were not more likely than controls to have another episode of overt GIB compared to controls during a follow-up of at least 3 years (Table 16). Another bleeding episode of overt bleeding was explained in 33%, 43% and 82% of unexplained overt, unexplained occult bleeders and controls, respectively (Table 16). A similar proportion of unexplained overt bleeders and controls were deceased at date of follow-up, whereas a greater proportion of unexplained occult bleeders were deceased compared to controls (p = 0.0015) (Table 16). However, those with unexplained occult GIB were older than controls, 68 (±16) and 65 (±18), although the difference was not statistically significant (p = 0.0699) (Table 16).

	Unexplained overt bleeders	**Unexplained occult bleeders**	**Controls**	***p -value***
n	118	113	320	
Follow-up time (±SD)	3.3 years (±1.06)	3.0 years (±1.56)	3.2 years (±1.21)	
A bleeding episode after initial endoscopy - % (n)	7 (8)	6 (7)	4.5 (14)	NS
Overt - % (n)	5 (6)	6 (7)	3.5 (11)	NS
Causes identified - % (n)	33 (2)	43 (3)	82 (9)	NS
Death - % (n)	19 (23)	37 (42)	22 (71)	0.015*

**Occult bleeders compared to controls*

Table 16. *A comparison of outcome in unexplained overt, unexplained occult bleeders and controls.*

4.5. Bleeding-related symptoms in colorectal cancer

Of the 472 bleeders diagnosed with colorectal cancer, 74% (348/472) had bleeding-related symptoms. Of those, 61% (*n* = 212) had overt bleeding and 39% (*n* = 136) had occult bleeding. The most common symptoms of the overall cohort were anemia (51%), rectal bleeding (44%), altered stools, constipation or diarrhea (37%), IDA (31%) and abdominal pain or discomfort (29%). Among overt bleeders, 97% had rectal bleeding, whereas 3% exclusively had melaena. Of the occult bleeders, 84% had IDA and 16% exclusively had a positive FOBT.

Patients with occult bleeding were more likely than non-bleeders to have proximal cancer, OR 3.0, and those with overt bleeding were much less likely to have proximal cancer compared to occult bleeders, OR 0.095 (Table 17). With regard to obstructive symptoms, only 2% of those with overt bleeding had obstructive symptoms compared to 16% of non-bleeders, OR 0.13 (Table 17). In all, 17% and 22% of patients with overt and occult bleeding had metastases at diagnosis, respectively (Table 17). A greater proportion of non-bleeders had metastases at diagnosis (35%) compared to overt and occult bleeders, OR 0.54 and 0.56, respectively (Table 17).

	Proximal cancer	Obstructive symptoms	Metastasis
Bleeding-related symptoms (n =348)	38%	5%	19%
Overt bleeders (n = 212)	17%	2%	17%
Occult bleeders (n = 136)	69%	9%	22%
Non-bleeders *(n = 124)*	42%	16%	35%
Bleeders vs. non-bleeders (*p-value)*	<0.0001	<0.0001	<0.05
Subgroup analysis	†, ‡, ☥	†, ‡	‡, ☥
Odds Ratio (Confidence Interval)			
Bleeders vs. non-bleeders	---	0.32 (0.16-0.66)	0.56 (0.35-0.91)
Overt vs. non-bleeders	0.32 (0.19-0.54)	0.13 (0.042-0.42)	0.54 (0.31-0.96)
Overt vs. Occult	0.095 (0.057-0.16)	0.15 (0.042-0.52)	---
Occult vs. non-bleeders	3.0 (1.8-5.1)	---	0.56 (0.31-0.99)

† = Significant difference between overt and occult bleeders ($p < 0.05$)

‡ = Significant difference between overt and non-bleeders ($p < 0.05$)

☥ = Significant difference between occult and non-bleeders ($p < 0.05$)

Table 17. *Prevalence of obstructive symptoms, proximal cancer and metastasis among CRC patients with bleeding-related symptoms and non-bleeders. All p-values are derived from a univariate analysis and odds ratios and confidence intervals are derived from multivariate analysis.*

5. Discussion

5.1. Incidence of acute and obscure gastrointestinal bleeding

The incidence of AUGIB was found to be 87/100,000 inhabitants *per* year. Previously, the incidence of AUGIB has been reported to range from 36-172/100,000 (Ahsberg et al., 2010; Blatchford et al., 1997; Button et al., 2011; Czernichow et al., 2000; Lanas et al., 2009; Longstreth, 1995; Loperfido et al., 2009; Paspatis et al., 2012; Paspatis et al., 2000; Rockall et al., 1995; Theocharis et al., 2008; Thomopoulos et al., 2004; van Leerdam et al., 2003; Yavorski et al., 1995). However, many of these studies were retrospective and identified bleeders by ICD codes which has been shown to capture only 62% of patients with AUGIB compared to prospective patient finding (Rockall et al., 1995). In recent years, three well designed prospective population-based studies have shown the incidence of AUGIB to be 90-108 *per* 100,000 inhabitants and year (Loperfido et al., 2009; Paspatis et al., 2012; Theocharis et al., 2008), similar to our results of 87/100,000 inhabitants *per* year. The incidence of AUGIB has been decreasing in the western world according to most time trend analyses (Lanas et al., 2009; Loperfido et al., 2009; Paspatis et al., 2012; Theocharis et al., 2008; van Leerdam et al., 2003) but not all (Button et al., 2011). This is most likely related to a decrease in the prevalence of peptic ulcer disease, due to decreased prevalence of *Helicobacter pylori* and increased use of PPIs along with NSAIDs (Lanas et al., 2009; Loperfido et al., 2009; Theocharis et al., 2008; van Leerdam et al., 2003). The similar incidence rates of AUGIB in recent studies may indicate that AUGIB incidence has reached its plateau after the decrease in recent decades.

The incidence of ALGIB reported in *Paper II* was 87/100,000 inhabitants *per* year, which is much higher than the previously reported incidence of 21-43/100,000 inhabitants and year (Ahsberg et al., 2010; Lanas et al., 2009; Longstreth, 1997). The reason for this difference in rates may partly be explained by two factors. Firstly, prior studies reporting the incidence of ALGIB have all been retrospective (Ahsberg et al., 2010; Lanas et al., 2009; Longstreth, 1997), which is likely to result in worse patient finding as has been shown in AUGIB (Rockall et al., 1995). Secondly, as AUGIB incidence has been reported to be decreasing, the incidence of ALGIB may be increasing (Lanas et al., 2009).

The incidence of obscure GIB has previously not been reported, the incidence rate in *Paper IV* was 10/100,000 inhabitants *per* year. The incidence of obscure GIB in patients 40 years and older was higher than for patients younger than 40 years and overt obscure GIB was more common than occult obscure GIB. Some causes of obscure GIB are age-dependent. For example, angiodysplasia and NSAID enteropathy have been found to be more common in patients older than 40 years of age, while tumors, Crohn's disease, Dieulafoy's lesion and Meckel's diverticulum have been found to be common in the younger patient groups (Raju et al., 2007).

5.2. Etiology of acute gastrointestinal bleeding

The most common cause of AUGIB was peptic ulcer, with a similar proportion of gastric and duodenal ulcers. This in accordance with recent studies reporting a proportion of 45-67% of PU in patients with AUGIB (Loperfido et al., 2009; Paspatis et al., 2012; Theocharis et al., 2008). Other common causes where oesophagitis and Mallory-Weiss tears, partly in line with other studies showing Mallory-Weiss tears to be an uncommon cause of AUGIB (Table 1). Angiodysplasia, gastric cancer and oesophageal varices were uncommon causes of AUGIB.

Regarding the etiology of ALGIB, diverticulosis was the most common cause of ALGIB as others have reported (Gayer et al., 2009; Longstreth, 1997; Makela et al., 1993). Ischemic colitis seems to be becoming one of the most common cause of ALGIB as recent studies suggest (Arroja et al., 2011). Inflammatory-bowel disease was a relatively common cause of bleeding compared to most other studies (Arroja et al., 2011; Longstreth, 1997; Makela et al., 1993), which may in part be explained by the fact that incidence of IBD is higher in Northern Europe compared Southern Europe (Burisch et al., 2013). About 7% of ALGIB patients were diagnosed with colorectal cancer and other causes, such as angiodysplasia, were relatively uncommon causes of ALGIB as in other studies (Arroja et al., 2011; Gayer et al., 2009; Longstreth, 1997; Makela et al., 1993).

5.3. The role of drugs in gastrointestinal bleeding

5.3.1. Drugs and AUGIB

The association of NSAIDs and AUGIB has been recognized for quite some time (Carson et al., 1987; Gabriel et al., 1991) and has been consistently confirmed since (Hernandez-Diaz & Rodriguez, 2000; Sostres et al., 2010). Our results are in agreement with this as NSAID use was independently associated with AUGIB, OR 2.1 (CI 1.1–4.1).

There is a considerable amount of data showing association between LDA and upper gastrointestinal bleeding (Garcia Rodriguez et al., 2011; McQuaid & Laine, 2006; Sorensen et al., 2000) although not as well established as the association of NSAIDs and AUGIB. Our results showed patients with AUGIB were more likely than controls to use LDA, which is in accordance with previous studies and contributes to the existing literature.

Warfarin use was found to be independently associated with AUGIB, OR 2.4 (CI 1.3–4.6) in *Paper I.* There is a paucity of studies investigating the association of warfarin and AUGIB in the general population and with focus on AUGIB. One population-based case-control study (Hallas et al., 2006) showed the OR of AUGIB in patients on K-vitamin antagonists to be 1.8 (CI 1.3 to 2.4), similar to results in *Paper I.*

5.3.2. Drugs and ALGIB

Non-steroidal anti-inflammatory drugs seem to be associated with ALGIB, although data are somewhat more limited (Chang et al., 2011; Holt et al., 1993; Lanas et al., 1992; Langman et al., 1985; Wilcox et al., 1997b). A prospective study, reported 105 patients with ALGIB to have an OR 2.0 (CI 1.3-3.2) of using NSAIDs compared to an older cohort of controls (Wilcox et al., 1997b). A recent retrospective, nationwide study in Taiwan, using ICD-9 codes for case finding, found patients with lower gastrointestinal bleeding to have greater odds than controls to use NSAIDs, OR 2.3 (CI 1.78-2.85) (Chang et al., 2011). Other studies have shown an association between ALGIB and NSAIDs, however, they did not distinguish between non-aspirin NSAIDs and aspirin (Holt et al., 1993; Lanas et al., 1992; Langman et al., 1985). In *Paper III,* ALGIB patients were more likely to use NSAID than controls, OR 3.5 (CI 2.00-6.08).

These results are an important addition to the above-mentioned data as the data were obtained in a prospective manner.

Low-dose aspirin may have relation with ALGIB as well (Holt et al., 1993; Huang et al., 2010, 2011; Lanas et al., 1992; Langman et al., 1985). Two prospective cohort studies, recently compared patients using aspirin ≥6 a week and nonusers (Huang et al., 2010, 2011). Aspirin-users were more likely to have ALGIB in both men, OR 1.34 (CI 1.00–1.79) (Huang et al., 2010), and women OR 1.55 (CI 1.15-2.09) (Huang et al., 2011). However, these studies, among other studies reporting aspirin to be associated with ALGIB (Holt et al., 1993; Lanas et al., 1992; Langman et al., 1985), did not differentiate between regular, and low-dose aspirin. Studies investigating LDA as a secondary prevention for cardiovascular disease usually focus on all bleeding events and rarely differentiate between upper and lower GIB. As previous studies investigating the association of LDA and ALGIB have not distinctly distinguished between low- and regular dose aspirin the results from *Paper III* are a significant addition to the theory that LDA may increase the risk of ALGIB.

The results of *Paper III* showed patients with ALGIB were more likely than controls to use warfarin OR 2.8 (CI 1.65-4.69). The data on this possible association are however scarce. A randomized controlled trial showed that 4% of warfarin users and 2% of LDA users had GIB (Hurlen et al., 2002), which may indicate that warfarin users are at least as likely as LDA users to experience GIB. Furthermore, a retrospective, population-based study performed in the UK, demonstrated the OR of warfarin use in patients with any GIB compared to controls was 2.6 (CI 2.31–3.03) (Delaney et al., 2007).

5.3.2.1. Drugs and specific etiology of ALGIB

Regarding drugs and specific etiology of ALGIB, NSAIDs and LDA have been shown to be associated with bleeding from diverticulosis (Kvasnovsky et al., 2013; Strate et al., 2011; Yuhara et al., 2013), as our results support. However, investigations on the association of warfarin and diverticular bleeding are lacking. Of four small studies examining this association, one reported a non-significant trend of warfarin use in patients with diverticular bleeding (Suzuki et al., 2012). The three remaining studies found no association (Jansen et al., 2009; Tsuruoka et al., 2011;

Yamada et al., 2008), which may be explained by a lack of statistical power as in the overall cohort of the studies; only 3 (Tsuruoka et al., 2011), 6 (Jansen et al., 2009), and 15 (Yamada et al., 2008) patients were using anticoagulants. In *Paper III,* an association of bleeding from diverticulosis and warfarin use was found, OR 2.7 (CI 1.26-5.59).

Although it has been proposed, it is still not clear whether the use of NSAIDs leads to flares in IBD (Feagins & Cryer, 2010). In *Paper III,* NSAID use was found to be more common in patients with bleeding caused by IBD, OR 3.4 (CI 1.17-9.57). This may denote that NSAIDs increase the risk of bleeding in IBD patients. However, *Paper III* was not designed to explore the association between use of NSAIDs and IBD flares.

In *Paper III,* patients with ischemic colitis were more likely than controls to use LDA, OR 2.3. There is a scarcity of studies investigating the association of LDA and bleeding caused by ischemic colitis. One study examining patients with ischemic colitis (with or without bleeding) found LDA use to be independently associated with ischemic colitis, OR 2.0 (CI 1.16-3.36) (Fernandez et al., 2010). These results are in accordance with the results from *Paper III,* although our study only included patients with ischemic colitis patients that bled. Patients with ischemic colitis are prone to have cardiovascular disease (Moszkowicz et al., 2013), which may confound the apparent association in *Paper III.*

5.3.3. Drugs and clinically significant bleeding

In *Paper I,* NSAIDs were shown to be associated with clinically significant AUGIB and in *Paper III,* NSAIDs, warfarin and the concomitant use of LDA and warfarin were associated with clinically significant ALGIB.

Most studies attempting to identify risk factors for outcome in AUGIB have not found NSAID to be associated with worse outcome (Blatchford et al., 2000; Corley et al., 1998; Marmo et al., 2008; Rockall et al., 1996). This is not in accordance with the results of *Paper I,* where NSAID use was identified as an independent predictor of clinically significant bleeding, OR 6.6 (CI 1.8–24). However, above-mentioned studies mostly focused on rebleeding rates and mortality

(Blatchford et al., 2000; Corley et al., 1998; Marmo et al., 2008; Rockall et al., 1996) and some did not note NSAID use (Blatchford et al., 2000).

Studies investigating the association of drugs and clinically significant ALGIB show conflicting results. A retrospective study investigating 123 patients with severe bleeding, found that aspirin use (any dosage) was an independent risk factor for severe bleeding when compared to 129 patients without severe bleeding, OR 2.1 (CI 1.12-3.82) (Strate et al., 2003). However, NSAIDs and anticoagulants were not associated with severe bleeding (Strate et al., 2003). A prospective study analyzing the effect of aspirin/NSAID use on outcome in 161 patients with ALGIB, found NSAID use not to be associated with differences in clinical presentation, transfusion requirements, rebleeding rate, requirement for surgery or mortality when compared to nonusers (Wilcox & Clark, 1997). A retrospective, nationwide study demonstrated that of 510 deaths caused by ALGIB in Spain, 36% (n = 185) were attributed to NSAID or aspirin use (Lanas et al., 2005). Of all deaths reported in the study, one-third were attributed to LDA use (Lanas et al., 2005). Some of these studies did not distinguish between aspirin (any dosage) or other NSAIDs (Lanas et al., 2005; Wilcox & Clark, 1997) and had a different definition of clinically significant ALGIB (Strate et al., 2003). Our results suggest that NSAID use increases the risk of clinically significant bleeding, OR 2.1 (CI 1.13-3.88), in contrast to other (Strate et al., 2003; Wilcox & Clark, 1997), but not all studies (Lanas et al., 2005). Furthermore, LDA was not associated with an increased risk of clinically significant bleeding, OR 1.5 (CI 0.90-2.52), in contrast to others (Lanas et al., 2005; Strate et al., 2003).

In *Paper III,* patients with clinically significant ALGIB had an OR 30.7 of concomitant LDA and warfarin use compared to non-clinically significant bleeders. Although there is lack of studies investigating this specific association, studies have shown that the risk of bleeding while on concomitant LDA therapy is higher than for LDA monotherapy (Delaney et al., 2007; Lanas et al., 2011) and warfarin monotherapy (Delaney et al., 2007; Hansen et al., 2010). Our results not only associate concomitant therapy of LDA and warfarin with ALGIB, but also strongly indicate that patients on this dual therapy are far more likely to have clinically significant bleeding if they experience a bleeding episode.

5.3.4. Drugs and unexplained bleeding

The possible association of drug use and unexplained bleeding is largely unexplored. Studies investigating patients with occult GIB have reported the prevalence of NSAID use to be 11-60% among these patients (Bampton & Holloway, 1996; Kepczyk & Kadakia, 1995; Rockey & Cello, 1993) and others have reported aspirin/NSAID use to be 22-33% (Stray & Weberg, 2006; Zuckerman & Benitez, 1992). None of these studies provided the prevalence of drug use among patients with unexplained occult GIB (Bampton & Holloway, 1996; Kepczyk & Kadakia, 1995; Rockey & Cello, 1993; Stray & Weberg, 2006; Zuckerman & Benitez, 1992). The results of *Paper IV* suggest that NSAIDs are associated with unexplained bleeding whereas LDA does not seem to have a major role in this type of bleeding. As previously described, warfarin seems to increase the risk of acute GIB (Delaney et al., 2007; Hurlen et al., 2002). The results from *Paper III* indicate warfarin may be associated with unexplained bleeding as well.

5.3.5. Drugs and colorectal cancer

In both *Papers III* and *V,* patients with bleeding caused by colorectal cancer did not seem more likely to use LDA compared to patients without bleeding. However, colorectal cancer patients with overt bleeding in *Paper V* were more likely to use warfarin compared to CRC patients without bleeding-related symptoms. Furthermore, patients with ALGIB caused by colorectal cancer in *Paper III* showed a trend towards warfarin use OR 2.8 ($p = 0.07$). This is in accordance to others showing that warfarin may induce bleeding in CRC (Asiimwe et al., 2013; Johannsdottir et al., 2012). This is noteworthy, as bleeding from colorectal cancer may prompt earlier diagnosis of the disease (Alexiusdottir et al., 2013).

5.4. Outcome of gastrointestinal bleeding

For patients with AUGIB, endoscopic treatment was required in 24%, slightly lower than in previous studies (Loperfido et al., 2009; Peura et al., 1997). This difference might due to the difference in study population as the current study was population-based and therefore more likely to reflect reliable data in “all comers” compared to patients from referral centers (Loperfido et al., 2009; Peura et al., 1997). The need for acute surgery in

this study was only 1.9%, the lowest proportion reported to date. This rate is similar to recent figures (Hearnshaw et al., 2011) and in accordance with the fact that acute surgery rates for AUGIB have been reported to be decreasing in the recent decades (Thomopoulos et al., 2004). The mortality rate of bleeding-related deaths in AUGIB patients has been found to be around 2.5% (Loperfido et al., 2009; Peura et al., 1997), similar to the 1.3% reported in *Paper I*.

Endoscopic therapy has been reported to be undertaken in 3-4% of ALGIB patients (Gayer et al., 2009; Longstreth, 1997; Makela et al., 1993), similar to the 7.4% of ALGIB patients requiring endoscopic hemostasis in *Paper II,* although some have reported higher rates (Arroja et al., 2011). In older studies the surgery rate of ALGIB has been reported to be 3-11% (Longstreth, 1997; Makela et al., 1993), but the rate is lower in more recent studies, or 1.4-4% (Arroja et al., 2011; Gayer et al., 2009). No patient in *Paper II* required surgery, which seems to confirm that surgery for ALGIB is very rare. The mortality from bleeding was found to be 1.2% which is in line with most recent studies reporting a bleeding related mortality rate of 0-4% (Arroja et al., 2011; Gayer et al., 2009; Green et al., 2005; Longstreth, 1997; Makela et al., 1993).

5.5. Bleeding-related symptoms in colorectal cancer

In *Paper V,* 74% of patients with colorectal cancer were found to have bleeding-related symptoms. Of, the total cohort, 44% had overt bleeding which is similar to the 37-58% range of other studies (Alexiusdottir et al., 2012; Cappell & Goldberg, 1992; Hamilton et al., 2005; Korsgaard et al., 2006; Majumdar et al., 1999; Stapley et al., 2006). However, studies examining what proportion of patients present with occult bleeding-related symptoms (IDA or a positive FOBT) in a nationwide setting are largely lacking. In *Paper V,* occult bleeders accounted for 29% of the total cohort and 39% of the patients with bleeding-related symptoms. These results show a clear proportion of occult bleeders among colorectal cancer patients and may offer an indication of how many patients can be captured *via* FOBT.

Patients with overt bleeding symptoms were less likely than those with non-bleeding-related symptoms to have metastases at diagnosis. There have been just a few studies investigating the relation of overt bleeding and survival (Alexiusdottir et

al., 2012; Alexiusdottir et al., 2013). These studies indicate that patients with overt bleeding have a lower TNM-stage at diagnosis (Alexiusdottir et al., 2012) and a better disease-specific survival (Alexiusdottir et al., 2013). Likewise, studies investigating the prognosis of CRC patients with occult bleeding are lacking. Studies have shown proximal cancer to be associated with a more advanced disease at diagnosis (Benedix et al., 2010; Meguid et al., 2008; Nawa et al., 2008; Shepherd & Jones, 1971; Snaebjornsson et al., 2010). In spite of this, CRC patients with occult bleeding in *Paper V* were less likely than controls to have metastases at diagnosins although a greater proportion of them had proximal cancer compared to controls (69% vs. 42%). This may in part be explained by the fact that the majority of patients with occult bleeding have IDA, which can prompt earlier diagnosis. However, that assumes patients that bleed have symptoms earlier than patients that do not bleed. Furthermore, this raises the question of whether patients that bleed are fundamentally different from patients that do not bleed.

5.6. Strengths and weaknesses

One of the main strength of this thesis is the prospective recruitment of patients in *Paper I-IV*. Although *Paper V* was retrospective, the study was nationwide and we can assume we found almost all patients in the country as the Icelandic Cancer Registry has been shown to have a very high completeness (Sigurdardottir et al., 2012). Another important strength of this thesis is the thorough drug history obtained by three different channels. Firstly, by endoscopic nurses interviewing patients prior to endoscopy, secondly, by medical chart review and lastly, *via* access to a nationwide pharmaceutical database. A limitation of the studies is that we did not systematically register co-morbidities, which would have improved the comparability of cases and controls. However, the prognosis of AUGIB and ALGIB was generally good which makes assessment of comorbidities less important. Another potential weakness is that we cannot exclude the possibility that some patients could have undergone surgery or had a bleeding-related death without undergoing endoscopy, this may make the surgery and mortality rates appear lower than in reality, if this happened.

6. Conclusions

Both acute upper and lower GIB are common events among the general population. In a population-based, prospectively registered cohort, the incidence for AUGIB and ALGIB was the same. This is in contrast with the common view among physicians that AUGIB is more common than ALGIB. These results may reflect a plateau in the incidence of AUGIB after a decrease in recent decades, as well as an increase in ALGIB incidence. The incidence for obscure GIB is much lower than for acute gastrointestinal bleeding.

The etiology of both AUGIB and ALGIB was mostly in accordance with previous studies. Although this thesis, and recent studies, indicate that ischemic colitis is becoming one of the most common cause of ALGIB.

The use of NSAIDs, LDA and warfarin seems to play a major role in gastrointestinal bleeding. Although the adverse effect of NSAIDs and perhaps LDA on the upper GI tract seems to be common knowledge among physicians, the awareness of possible lower GI effects seems to be lacking. The results of this thesis indicate that physicians should keep in mind that NSAIDs and LDA also have possible adverse effects on the lower gastrointestinal tract. Furthermore, physicians may associate warfarin use with increased risk of GIB. However, this has not been properly quantified with regard to AUGIB and ALGIB specifically, the results presented in this thesis give an indication of that risk. In addition, some of these drugs and/or combination of drugs may increase the risk of clinically significant bleeding. Data on this possibility may aid physicians in assessing the risk/benefit ratio of drug therapies in certain situations. Lastly, warfarin may induce bleeding in CRC patients, resulting in an earlier diagnosis.

The outcome of GIB is favorable as long-term rebleeding rates among patients with unexplained GIB are low and with regard to short-term outcome in patients with acute GIB, the need for acute surgery and bleeding-related deaths are rare.

Of patients with colorectal cancer, three fourths present with bleeding-related symptoms. These data aid in concluding on what proportion of CRC patients may be captured *via* FOBT. Our data also suggest that patients with bleeding-related symptoms present earlier than non-bleeders, suggesting a better prognosis for bleeders.

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