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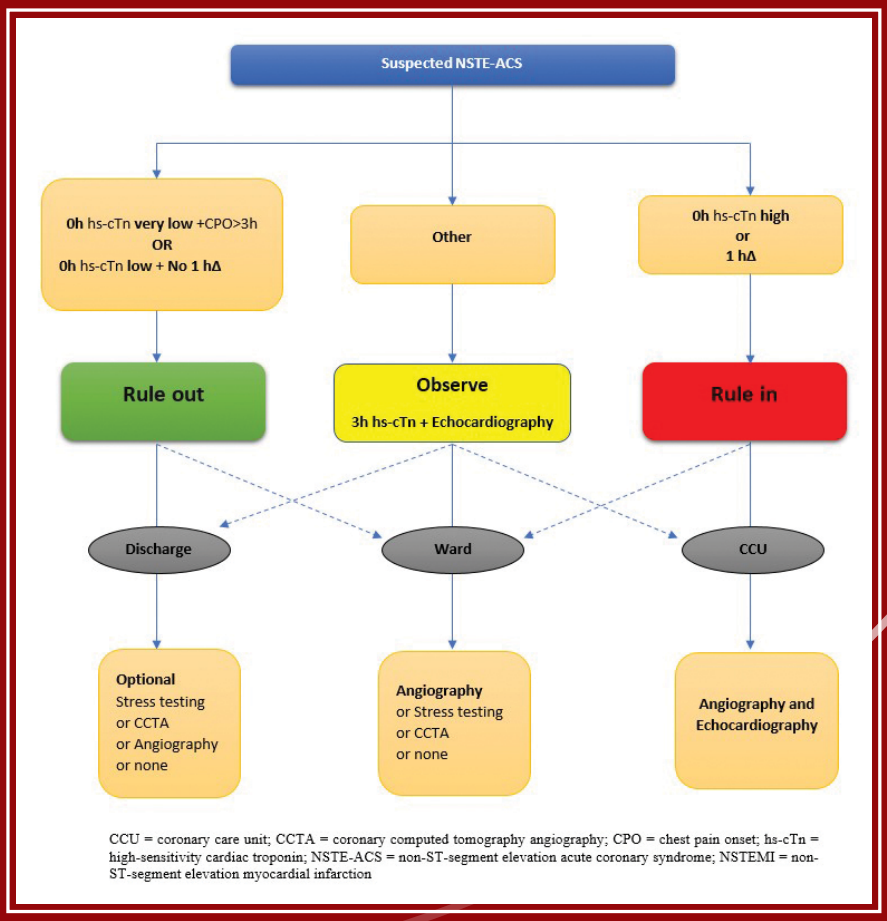

Algorithm for suspected acute coronary syndrome (ACS)

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MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS

42 Votsi Street, Patras 26221, Greece
Tel: +30 2610 279579, Fax: +30 2610 220518
email: iede_pel@yahoo.gr

Publisher
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Editor-in-Chief
Christos Triantos
email: achaiki.iatriki@gmail.com

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ACHAIKI IATRIKI

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CONTENTS

Dear colleagues,

Happy new year full of happiness, peace, and success !

In the current issue, the editorial by Conti, et al. provides an updated overview of the emerging therapies for inflammatory bowel diseases and highlights the need of personalized medicine. Moreover, this issue includes five review articles. The first review, by Amptoulach S. summarizes the latest data regarding the systematic treatment of metastatic esophagogastric adenocarcinoma (EGAC) and esophageal squamous cell carcinoma (ESCC), discusses the updates in the molecular targeted agents and summarizes significant locally advanced and metastatic EGAC- and ESCC-related clinical trials. The review by Travlos et al. provides the current knowledge concerning the use of new oral anticoagulants in the prevention of thromboembolic events in patients with atrial fibrillation. The review by Balta L. describes the advances in the classification of patients with chronic kidney disease (CKD) and demonstrates the prerequisites for achieving the optimal outcomes for CKD patients. The review, by Moulias et al. presents data on the high sensitivity cardiac troponin assays diagnostic utility and summarizes primary principles for their appropriate, safe and effective use in clinical practice. Lastly, the review by Lagadinou et al. provides a general overview of the diagnostic approach of fever in people living in rural areas, highlighting the need of health workers' proper training since early diagnosis and proper treatment are critical.

Lastly, it is with great pleasure that I introduce our new Editorial Board members for the years 2023-2024. Thank you all for participating !

C. Triantos
Associate Professor in Internal Medicine
and Gastroenterology Faculty of Medicine,
School of Health Sciences, University of Patras
Editor-in-Chief of the journal "ACHAIKI IATRIKI"

New drugs in Inflammatory bowel disease

Kelly Conti, Pierre Ellul

Inflammatory bowel disease (IBD) is an immune mediated condition with a progressive or relapsing and remitting disease course. IBD can be categorized broadly into Crohn`s Disease (CD) and Ulcerative Colitis (UC). Though these conditions primarily affect the gastrointestinal tract, extra-intestinal manifestation have been reported to occur in up to 55% of CD and 35% UC patients [1,2]. Furthermore, CD can also lead to intestinal strictures, abscesses and fistulas. Uncontrolled inflammation can also lead to an increased risk of malignancy. The pathogenesis of IBD is multifactorial with various factors postulated to affect the disease course. The better understanding of these pathologies has led to new therapeutic modalities.

Nowadays, our routine daily therapeutic arsenal, apart from aminosalicylates includes a variety of biologicals and small molecules: thiopurines, methotrexate (CD only), monoclonal antibody against tumor necrosis factor α [TNF-α]), an IgG1 antibody which blocks the α4β7 integrin which is gut selective (vedoluzimab), an IgG monoclonal antibody which binds to the p40 subunit of interleukins 12 and 23 (ustekinumab) and a Janus kinase (JAK) inhibitor (tofacitinib) for patients with UC.

Over time, some of these drugs also obtain new indications. Recent studies have shown that vedoluzimab has showed promising results in the treatment of resistant pouchitis [3].

However, though we have these drugs available, we still have a subset of patients who either fail to enter remission or develop loss of response to the available drugs. These cases are known as primary or secondary non-responders. Up to a third of patients may have primary non-response to biologicals and up to 50% of patients develop either a secondary loss of response or a serious adverse event necessitating the discontinuation of medications [4].

Division of Gastroenterology, Mater Dei Hospital, Malta
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This has led to the analysis of pathway mechanisms involved and thus the development of new drugs. The following medications offer hope both for the physician and even more for the patient. These drugs are summarised in Table 1.

Table 1.

Drug	Mechanism of Action
Upadacitinib	JAK-1 inhibitor
Filgotinib	JAK-1 inhibitor
Risankizumab	Monoclonal antibody directed against the p19 subunit of IL-23
Mirikizumab	Monoclonal antibody directed against the p19 subunit of IL-23
Brazikumab	Monoclonal antibody directed against the p19 subunit of IL-23
Guselkumab	Monoclonal antibody directed against the p19 subunit of IL-23
Etrasimod.	Sphingosine 1 phosphate receptor modulators
Ozanimod	Sphingosine 1 phosphate receptor modulators
Ontamalimab	Anti- mucosal addressin cell adhesion molecule-1 Monoclonal Antibody

JAK: Janus kinase; IL: interleukin

JAK Inhibitors

Tofacitinib, which is a JAK1 and JAK 3 inhibitor, is licensed for patients with UC. Upadacitinib (UPA) is a JAK1 selective inhibitor which is being studied for use in IBD.

UPAs action is associated with the down regulation of various proinflammatory cytokines which include the following interleukins: IL-2, 4, 6, 7, 9, 15, 21, and

Key words: *Drugs; refractory; Crohn`s disease; ulcerative colitis; inflammatory bowel disease*

interferon gamma (IFN-γ) which are implicated in the pathogenesis of IBD.

Viral reactivations and infections such as herpes simplex are documented as potential adverse effects of all JAK inhibitors. Tofacitinib is associated with an increased risk of thrombosis and further studies are needed to assess this risk with UPA [5].

Data from rheumatoid arthritis demonstrated that the risk of infection was higher with tofacitinib when administered at 10 mg, twice daily (RR: 2.75; 95% CI, 1.72 to 4.41) compared to upadacitinib, 15 mg, daily (RR: 1.35; 95% CI, 1.14 to 1.60) [6].

UPA may play a role in patients who have failed to respond to conventional IBD treatment.

UPA was evaluated in a phase 3, multicentre, randomised, double-blind, placebo-controlled clinical programme which consisted of two replicate induction studies (U-ACHIEVE induction [UC1] and U-ACCOMPLISH [UC2]) and a single maintenance study (U-ACHIEVE maintenance [UC3] in UC patients.

Statistically significantly more patients achieved clinical remission with upadacitinib 45 mg (26% of patients in UC1; 34% of patients in UC2) than in the placebo group (5% of patients in UC1 and 4% of patients; p<0.0001).

In the maintenance study, clinical remission was achieved by statistically significantly more patients receiving upadacitinib [15 mg (42%); 30 mg (52%)] than those receiving placebo (12%; p<0·0001). The most commonly reported adverse events in UC1 were nasopharyngitis (5% of patients in the upadacitinib 45 mg group vs 4% of patients in the placebo group), creatine phosphokinase elevation (4% vs 2%), and acne (5% vs 1%). In UC2, the most frequently reported adverse event was acne (27% of patients in the upadacitinib 45 mg group vs 2% in the placebo group). In UC3, the most frequently reported adverse events (≥5%) were worsening of UC (13% of patients in the upadacitinib 15 mg group vs 7% of patients in the upadacitinib 30 mg group vs 30% of patients in the placebo group), nasopharyngitis (12% vs 14% vs 10%), creatine phosphokinase elevation (6% vs 8% vs 2%), arthralgia (6% vs 3% vs 10%), and upper respiratory tract infection (5% vs 6% vs 4%) [7].

UPA treatment is also effective in resolving extraintestinal manifestations (EIMs) in UC patients. Results from the UPA Phase 3 programme demonstrated a higher number of EIM symptom resolution compared to placebo following induction treatment with UPA 45 mg and after maintenance treatment with UPA 15 or 30 mg. However only the 30 mg dose provided a statistically significant improvement when compared to placebo (p<0.001) [8].

In the CELEST phase 2 study, patients were randomly assigned to either receive UPA or placebo, no comparison was made to other conventional treatment for CD. UPA was shown to induce clinical (p<0.10) and endoscopic remission (p<0.01) at week 16 in CD patients compared to placebo [5].

The JAK1 inhibitor filgotinib was found to have a higher fistula response (47.1% vs placebo 25%) and remission rates (47.1% vs placebo 16.7%) after 24 weeks of 200mg once daily dosing [9]. Filgotinib at a once daily dose was also found to be effective in inducing (26.1% vs placebo 15.2%) and maintaining remission at week 58 (23.8% vs placebo 13.5%) in patients with moderate to severe UC [10].

IL-23 inhibitors

Though, ustekinumab is licensed for the treatment of IBD, further studies are being performed on other interleukin (IL-) inhibitors. One such selective IL-23 inhibitor is Risankizumab (RZB) which binds to the p19 subunit.

In both ADVANCE and MOTIVATE induction studies, patients were assigned to either risankizumab 600 mg, risankizumab 1200 mg or placebo. The primary analysis population comprised 850 participants in ADVANCE and 569 participants in MOTIVATE. All coprimary endpoints at week 12 were met in both trials with both doses of risankizumab (p ≤0.0001).

In ADVANCE, CDAI clinical remission rate was 45% (adjusted difference 21%, 95% CI 12-29; 152/336) with risankizumab 600 mg and 42% (17%, 8-25; 141/339) with risankizumab 1200 mg versus 25% (43/175) with placebo; endoscopic response rate was 40% (28%, 21-35; 135/336) with risankizumab 600 mg and 32% (20%, 14-27; 109/339) with risankizumab 1200 mg versus 12% (21/175) with placebo.

In MOTIVATE, CDAI clinical remission rate was 42% (22%, 13-31; 80/191) with risankizumab 600 mg and 40% (21%, 12-29; 77/191) with risankizumab 1200 mg versus 20% (37/187) with placebo; and endoscopic response rate was 29% (18%, 10-25; 55/191) with risankizumab 600 mg and 34% (23%, 15-31; 65/191) with risankizumab 1200 mg versus 11% (21/187) with placebo.

The overall incidence of treatment-emergent adverse events was similar among treatment groups in both trials. Three deaths occurred during induction (two in the placebo group [ADVANCE] and one in the risanki-

zumab 1200 mg group [MOTIVATE]). The death in the risankizumab-treated patient was deemed unrelated to the study drug [11].

In the FORTIFY maintenance study, patients were randomly assigned to either the risankizumab 180 mg, risankizumab 360 mg group or the placebo group.

Greater clinical remission and endoscopic response rates were reached with 360 mg risankizumab versus placebo (CDAI clinical remission: 52% vs 41%; endoscopic response: 47% vs 22%). Higher rates of CDAI clinical remission (55%) and endoscopic response (47%) were achieved with the 180mg dose [12]. There are currently ongoing trials to assess its use in UC.

Mirikizumab (MIRI) is a humanized, IgG4 monoclonal antibody directed against the p19 subunit of IL-23 [13]. The Phase 3 LUCENT-1 study assessed the efficacy and safety of mirikizumab as induction therapy in patients with moderately to severely active UC. A significantly greater proportion of patients treated with MIRI achieved clinical remission at Week 12 (MIRI: 24.2% vs placebo: 13.3%; p=0.00006) with an improvement in other secondary endpoints (p<0.00001) [14, 15].

In a study with CD patients, Mirikizumab effectively induced endoscopic response after 12 weeks in patients with moderate-to-severe CD and demonstrated durable efficacy to Week 52.

At Week 12, endoscopic response was significantly higher for all mirikizumab groups (200, 600, or 1000 mg) compared with placebo (200 mg: 25.8%, p=0.079; 600 mg: 37.5%, p= 0.003; 1000 mg: 43.8%, p<0.001; placebo: 10.9 %). Endoscopic response at Week 52 was 58.5% in the intravenous group and 58.7% in the subcutaneous SC group [16].

Brazikumab (MEDI2070) is another monoclonal antibody targeting IL-23. In a phase 2 trial brazikumab was shown to achieve clinical remission at week 8 in 49.2% of patients with severely active CD compared to placebo (p=0.01), with a greater response being noted at week 12 [17].

Guselkumab (GUS), is an IL-23 p19 subunit antagonist. In the QUASAR Induction Study (phase 2b randomized, double-blind, placebo-controlled) its efficacy and safety were evaluated in patients with moderately to severely active UC who had an inadequate response or intolerance to conventional (thiopurines or corticosteroids) or advanced therapy (TNFα antagonists, vedolizumab, or tofacitinib).

At Week 12, a significantly greater proportion of patients treated with GUS 200 mg and 400 mg achieved clinical response compared with placebo (61.4% and 60.7% vs 27.6%, respectively, both p<0.001). The proportion of patients reporting adverse events, serious adverse events and adverse events leading to discontinuation in the GUS groups were not greater compared with placebo with no serious infections, malignancy and death being reported for GUS [18].

The phase 2 GALAXI 1 study assessed the clinical efficacy and safety of GUS maintenance therapy, using different dosages in patients with moderately to severely active CD through week 48.

The proportion of patients achieving clinical remission at week 48 ranged from 57.4-73.0% among GUS dose groups, with the vast majority of patients in clinical remission being also in corticosteroid-free remission at week 48 (55.7-71.4%). Key safety event rates were similar among GUS dose groups with no opportunistic infections, tuberculosis, or deaths being reported in any group [19].

Sphingosine 1 phosphate receptor modulators

A drug which is targeting a different pathway is etrasimod. This drug is a selective sphingosine 1 phosphate receptor (S1P) modulator which is administered as an oral preparation. S1P is expressed on lymphocytes and plays a vital role in lymphocyte trafficking.

The administration of etrasimod in patients with moderate to severe UC and at a dose of 2mg daily showed significant clinical improvement (p=0.009) and endoscopic improvement (p=0.003) compared to placebo.

An open-label extension study evaluated safety and efficacy of etrasimod for up to 52 weeks. At the end of the study clinical response was met in 64% of patients, 33% of patients were in clinical remission, and 43% demonstrated endoscopic improvement. In those patients who at week 12 had clinical response, clinical remission, or endoscopic improvement, these effects were maintained to end of treatment in 85%, 60%, or 69% of patients [20].

The use of etrasimod is advantageous as it is a once daily oral dose. Given that it is a small molecule, no immunogenicity is anticipated. Overall treatment with etrasimod was well tolerated, with fewer than 10% of patients discontinuing the drug. Treatment emergent adverse effects reported were mild to moderate in severity. The most commonly reported included nasopharyngitis, upper respiratory tract infections and anaemia [21].

Ozanimod is another selective sphingosine-1-phosphate receptor modulator, administered as an oral formulation. In a randomized, double-blind, placebo-controlled trial of ozanimod as induction and maintenance therapy in patients with moderately to severely active UC, clinical remission was significantly higher among patients who received ozanimod than among those who received placebo during both induction (18.4% vs. 6.0%, p<0.001) and maintenance (37.0% vs. 18.5% [among patients with a response at week 10], p<0.001).

The incidence of clinical response was also significantly higher with ozanimod than with placebo during induction (47.8% vs. 25.9%, P<0.001) and maintenance (60.0% vs. 41.0%, p<0.001). The incidence of any infection with ozanimod was similar to that with placebo during induction but higher than that with placebo during maintenance. Serious infection occurred in less than 2% of the patients and elevated liver aminotransferase levels were more common with ozanimod [22].

STEPSTONE was a phase 2, uncontrolled, multicentre trial in adults with moderately to severely active CD. At week 12, a reduction from baseline in Crohn's Disease Activity Index (CDAI) score was observed (mean change -130.4 [SD 103.9]) in 39.1%, of patients and response (CDAI decrease from baseline ≥100) in 56.5% of patients. Currently there are Phase 3 placebo-controlled trials [23].

Anti-MAdCAM-1 (mucosal addressin cell adhesion molecule-1) Monoclonal Antibody

Ontamalimab (SHP647), is a fully human immunoglobulin G2 monoclonal antibody against mucosal addressin cell adhesion molecule-1. OPERA II, is a multicenter, open-label, phase 2 extension study, assessing the long-term safety and efficacy of ontamalimab in patients with moderate-to-severe CD. The most common adverse event leading to study discontinuation was CD flare (19.8%). Two patients died and these incidents were not considered to be drug related. The inflammatory biomarker concentrations decreased. Remission rates (Harvey-Bradshaw Index [HBI] ≤ 5; baseline, 48.1%; week 72, 37.3%) and response rates (baseline [decrease in CDAI ≥ 70 points], 63.1%; week 72 [decrease in HBI ≥ 3], 42.5%) gradually decreased [24].

In Opera the use of this drug did not demonstrate any efficacy at any clinical endpoint compared with placebo [25].

TURANDOT II was a phase 2, multicentre, open-label study in patients with moderate-to-severe UC. The primary objective was safety. Mucosal healing was also assessed. Overall, 36.1% experienced drug-related adverse events, 5.5% of patients had serious infections, the most common being gastroenteritis (0.9%). One death and 4 cancers occurred and were considered to be unrelated to ontamalimab. Mucosal healing increased from 20.3% at baseline to 28.5% at week 16 and was maintained until week 144 of follow-up [26].

Unfortunately, currently no cure is available for IBD. Choosing the most appropriate drug can also be challenging for the physician especially when one has to even consider the economic burden, side-effect profile and response rate. Though having various drugs enables both the physician and the patient to have more medical options, choosing the right drug at the right time for a particular patient is challenging. The next step that is required is advancing personalised medicine – obtaining the scientific knowledge and biomarkers in order to choose the right drug for the right patient. However, in the meantime, knowing that new drugs may become available offers much needed hope for all patients and more particularly for those with severe IBD and perianal fistulating disease.

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Corresponding author:

Pierre Ellul Professor, MD PhD
Division of Gastroenterology, Mater Dei Hospital, Malta
E-mail: ellul.pierre@gmail.com

Modern systemic treatment of gastric and esophageal cancer

Sousana Amptoulach

Abstract

Esophageal cancer (EC) and gastric cancer (GC) are leading causes of cancer-related mortality worldwide with an increasing incidence and a poor prognosis. The management of these aggressive tumors is complex and often involves multimodality treatment including surgery, chemotherapy, and radiation. Despite advances in the management of upper gastrointestinal cancers, the biology of these tumors is complex. When EC and GC are advanced (locally or metastatic), chemotherapy remains the primary treatment and improves survival over best supportive care. The treatment of advanced EC and GC has been reshaped over the last years with the approval of several immune checkpoint inhibitors (ICIs) and mainly monoclonal antibodies targeting either the axis PD-1/PD-L1 or CTLA-4. The purpose of this review is to provide a summary of systematic treatment, to discuss updates in the molecular targeted agents and summarize significant clinical trials of locally advanced and metastatic esophagogastric adenocarcinoma (EGAC) and esophageal squamous cell carcinoma (ESCC). Due to the dynamic nature of this field, this review is not meant to be all-inclusive but rather to report the major established treatments.

Key words: *Immunotherapy; esophageal neoplasms; stomach neoplasms*

INTRODUCTION

Esophageal cancer (EC) is the eleventh most common cause of cancer worldwide and the sixth most common cause of cancer-related mortality [1]. The two major histologic subtypes of esophageal cancer are adenocarcinoma (EAC) and squamous cell carcinoma (ESCC). It is well-known that the incidence of both subtypes varies among geographic areas: SCC has a higher prevalence in East Asia, Eastern and Southern Africa, and Southern Europe, whereas AC is much more common in North America and other parts of Europe [2]. On the other hand, gastric cancer (GC) is the fifth most common and the third most lethal cancer worldwide [3]. Both, EC and GC, are often diagnosed at an advanced stage mainly due to the lack of early clinical symptoms. GCs can be classified into two types: early stage and advanced stage. According to the eighth edition of the American Joint Committee on Cancer TNM (8th AJCC TNM) system, early-stage gastric cancer is limited to the mucosa or submucosa regardless of the size of the lesion and the presence of lymph node metastasis. Tumors that infiltrate into or beyond the subserosa and extend to surrounding organs or metastasize are considered as advanced GC. Meanwhile, locally advanced cancer of the esophagus (stages IIb to IIIc) includes tumors that invade regional lymph nodes (N1-3) or local structures (T4 disease) [4]. Despite the recent increase in therapeutic options, responses to systemic therapies in patients with esophagogastric cancer are most often short-lived, and less than 5% of patients with metastatic disease survive beyond 5 years [5].

Division of Oncology, Department of Medicine, University Hospital of Patras, Patras, Greece

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Systemic therapy for metastatic esophageal adenocarcinoma and gastric carcinoma

First-line systemic therapy

Systemic therapy for metastatic EAC has been based on a study which included patients with gastric ad-

enocarcinomas. Although there are global variations, the standard doublet in the first-line setting is fluoropyrimidine (5-fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin [6]. For patients with HER2-positive EAC, adding trastuzumab to fluoropyrimidine plus platinum is recommended in the first-line setting based on the ToGA trial which has shown to improve outcomes [7]. Other molecular targeted drugs were assessed, but no additional targeted agents were found to be beneficial for EAC as first-line therapy at this point in time [7]. Intensifying treatment by adding a third drug is controversial. The only 3-drug regimen that has demonstrated superiority in a phase 3 study is DCF (docetaxel, cisplatin, and 5-FU). DCF resulted in modestly increased response rate (RR) and overall survival (OS) over cisplatin/5-FU but was associated with significant toxicity [8].

Second-line or subsequent systemic therapy

Ramucirumab plus paclitaxel is the preferred regimen for second-line therapy based on the RAINBOW study. In this phase III study, Ramucirumab combined with paclitaxel improved RR (28% vs 16%; *P* =0.0001), progression free survival (PFS), and OS (9.6 vs 7.4 months; *P* =0.017) versus paclitaxel alone [9]. Ramucirumab monotherapy is an option for patients who are not candidates for combination therapy with paclitaxel [10]. Single-agent irinotecan or taxane (docetaxel or paclitaxel) are associated with a modest improvement in median OS over best supportive care (BSC) alone with no apparent difference in efficacy between irinotecan versus taxane [11]. Recently, the phase III TAGS trial evaluated the efficacy of TAS-102, an orally administered combination of a thymidine based nucleic acid analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, in metastatic gastric and EGJ adenocarcinoma as third-line therapy [12]. A total of 507 patients were randomly assigned to the trifluridine/tipiracil group (n = 337) and to the placebo group (n = 170). Median OS was 5.7 months in the trifluridine/tipiracil group and 3.6 months in the placebo group (HR 0.69; 95% CI 0.56–0.85; P = 0.00058). Thus, TAS-102 was approved as an option for third-line therapy. However, only a select population might be suitable for TAS-102 because of the lack of response rate.

Immunotherapy in gastric cancer

In the last decade, immunotherapy has revolutionized the oncology landscape by targeting the host immune system. Cancer cells have the ability to evade the anti-tumor immune response by expressing PD-L1 (programmed cell death ligand 1) on the cell surface which inhibits the cytotoxic T-cells through binding and blockade of the T-cell receptor PD-1 (programmed cell death receptor 1). By overexpression of PD-L1 on their surface or inducing PD-L1 expression on immune cells, cancer cells exploit the PD-1/PD-L1 pathway to further promote immune escape and tumor growth. Furthermore, cancer cell-mediated upregulation of CTLA-4 (anti-cytotoxic T-lymphocyte-associated antigen 4) on T-cells enhances the recruitment of immunosuppressive T-cells and constitutes a co-inhibitory pathway to elude host immune responses. Blocking immune checkpoint such as programmed cell death protein 1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte antigen 4 (CTLA-4), has emerged as a new treatment strategy in several solid cancers [13].

Immunotherapy has also been added to HER2-directed therapy. In a phase III double-blind trial KEYNOTE-811 it was demonstrated that the addition of pembrolizumab to trastuzumab and chemotherapy significantly improved objective response rate in HER2-positive gastric cancer suggesting that there may be a synergistic benefit of combining checkpoint blockade with standard trastuzumab plus chemotherapy. Objective response was observed in pembrolizumab group compared with the placebo group (74.4% vs 51.9%, p≥ 0.00006) and complete responses were more frequently observed in the pembrolizumab group than in the placebo group (11.3% vs 3.1%) [14].

Assessment of microsatellite instability (MSI) status and programmed death ligand 1 (PD-L1) expression is recommended. In gastric cancer, deficiency mismatch repair gene (dMMR tumors) represent around 20% of patients, however, MSI tumors are rare in EC, and PD-1 or PD-L1 blockade is marginally effective in EAC. Since 2017, pembrolizumab has been approved as a second-line regimen for patients with MSI-high/deficient mismatch repair (MMR) solid tumors, regardless of tumor type, based on several trials, such as KEYNOTE-016 [15], KEYNOTE-164 [16], KEYNOTE-012 [17], KEYNOTE-028 [18], and KEYNOTE-158 [19]. Le et al., reported that objective radiographic response (ORR) was observed in 53% of patients, and complete response was achieved in 21% of patients with deficient MMR tumor [20]. The KEYNOTE-059 study showed that ORR was as high as 57% in patients with MSI-high tumors, which is significantly higher than the 9% in the case of microsatellite stable tumors [21]. The MMR status seems to be a helpful tool to better

select patients who may benefit from immunotherapy.

Another biomarker that is currently under investigation is TMB (tumor mutations burden). TMB quantifies the number of somatic mutations per coding area of a genome. It has been hypothesized that a heavily mutated tumor can produce a large number of neoantigens, resulting in T-cell infiltration and potentially increased responsiveness to checkpoint blockade. In June 2020, the FDA granted accelerated approval for the treatment of patients with unresectable or metastatic TMB-high (TMB-H) (≥10 mutations per megabase) solid tumors that progressed after prior treatment and had no satisfactory alternative treatment options. This was based upon a prospectively planned retrospective analysis of previously treated patients with advanced solid tumors and TMB-H enrolled on KEYNOTE-158. In this nonrandomized trial, of 790 evaluable patients, 102 (13%) were had TMB-H status and an ORR of 29% [22].

Nivolumab is another humanized monoclonal antibody that inhibits PD-1. In the randomized CheckMate-649 trial, the largest international phase III trial with 1581 patients suffering from locally advanced or metastatic Her2/neu negative adenocarcinoma of the gastroesophageal junction or stomach the effect of nivolumab plus chemotherapy (XELOX (capecitabine plus oxaliplatin) or FOLFOX (5-FU, folinic acid, oxaliplatine) versus chemotherapy alone was evaluated as the first-line regime. The results of the prespecified interim analysis of OS and PFS in this study were presented at ESMO 2020. The combination of nivolumab plus 5-FU/oxaliplatin significantly improved OS and PFS in patients with PD-L1 CPS ≥ 5 (primary endpoint, $n = 955$ patients, 60%). Improvement of median OS was 14.4 months versus 11.1 months (HR 98% CI = 0.71 (0.59–0.86), $p < 0.0001$). Differences were also statistically significant for all patients with PD-L1 CPS ≥ 1 (HR = 0.77, $p = 0.0001$) and for all randomly assigned patients irrespective of their PD-L1 CPS score (HR = 0.80, $p = 0.0002$). Because 70% of all patients have CPS ≥ 1 and 60% CPS ≥ 5, the positive results for these groups are likely to be driven by the CPS ≥ 5 population. In the group of patients with PD-L1 CPS ≥ 5, the median progression-free survival was 7.7 versus 6.0 months, respectively (HR 98% CI = 0.68 (0.56–0.81), $p < 0.0001$) [23]. Based on the results of this trial, the implementation of nivolumab as a first-line therapy option for advanced GEJ or stomach cancer with PD-L1 CPS ≥ 5 is now approved.

In the phase III, ATTRACTION-2 trial, evaluated the efficacy of nivolumab in patients with advanced gastric or EGJ adenocarcinoma who underwent at least two previous chemotherapy regimens. Here, 493 patients were randomly assigned to receive nivolumab (n = 330) or placebo (n = 163) [24]. Median OS was 5.26 months in the nivolumab group and 4.14 months in the placebo group (HR 0.63; 95% CI 0.51–0.78; P<0.001). Moreover, the survival benefit with nivolumab was independent of PD-L1 expression. Thus, nivolumab is accepted as third-line therapy regardless of PD-L1 expression in Japan. (Table 1: list of currently approved immune check point inhibitors).

Systemic therapy for advanced ESCC

First-line systemic therapy

As with EAC, fluoropyrimidine (5-fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin has been the most commonly used first-line regimen for advanced ESCC [25]. In the presidential session at ESMO 2020, the combination of pembrolizumab with CF as first-line treatment (a Phase III trial -KEYNOTE-590) showed a significant improvement in the overall survival in patients with ESCC. In the KEYNOTE-590 trial, a randomized international double-blind phase III study of pembrolizumab plus chemotherapy (cisplatin + 5-FU) versus chemotherapy alone, 749 patients with locally advanced or metastatic esophageal cancer (including Siewert type 1 adenocarcinoma of the esophago-gastric junction) were randomized 1:1 with 73% ESCC and 25% EAC patients. Independent of CPS (combined positivity score) and tumour histology, there was a significant benefit in OS (overall survival) in the combination group of pembrolizumab plus chemotherapy [OS all patients (pts) 12.4 vs. 9.8 months, HR 0.73 (95% CI 0.62–0.86, $p < 0.0002$); PFS (progression-free survival) all pts 6.3 vs. 5.8 months, HR 0.65 (95% CI 0.55–0.76)]. In particular, ESCC patients with CPS ≥ 10 benefitted most from the combination of immune checkpoint inhibition and chemotherapy (median OS 13.9 vs. 8.8 months, HR 95% CI = 0.57 (0.43–0.75), $p = 0.012$). The CPS score seems to be decisive for response in subgroups [26].

Second-line or subsequent systemic therapy

Single-agent chemotherapy with taxanes or irinotecan is an option for second-line therapy [27-29]. However, results with second-line chemotherapy in ESCC are inferior to those in EAC.

Immune checkpoint inhibitors have been approved as second line or subsequent therapy for advanced ESCC. Pembrolizumab has been accepted as a second-line ther-

Table 1. *Overview of approval of immune checkpoint inhibitors in oesophago-gastric cancer.*

Indication	Pembrolizumab	Nivolumab
Gastric	• 1st line Pebrolizumab/ trastuzumab/chemo for patients with advanced GC/GEJC/EAC HER2 + • Recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma expressing PD-L1 (CPS ≥ 1) with PD on or after ≥ 2 previous therapies including fluoropyrimidine- and platinum-containing chemotherapy ± HER2-targeted therapy	1st line NIVO+chemo for patients with advanced GC/GEJC/EAC with HER2(negative), expressing PD-L1 (CPS≥5)
Esophageal	• 1st line pebrolizumab/chemo in locally advanced or metastatic esophageal carcinoma including EGJ adenocarcinoma • Recurrent locally advanced or metastatic esophageal squamous cell carcinoma expressing PD-L1 (CPS ≥ 10) with PD after ≥ 1 previous lines of systemic therapy	Unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after previous fluoropyrimidine- and platinum-based chemotherapy
Tumor agnostic	Unresectable or metastatic **MSI-H or MMR deficient** solid tumors progressing after previous treatment with no satisfactory alternative treatment options Unresectable or metastatic **TMB≥10mut/Mb**) solid tumors progressing after previous treatment with no satisfactory alternative treatment options	

Abbreviations: CPS, combined positive score; GEJ, gastroesophageal junction; MMR, mismatch repair; MSI-H, microsatellite instability-high; PD, progressive disease; TMB-H, tumor mutational burden-high.

apy for patients with advanced ESSC with PD-L1 expression levels by CPS of >10. The phase III KEYNOTE-181 trial compared pembrolizumab versus investigator's choice chemotherapy (docetaxel, paclitaxel, or irinotecan) as second-line therapy in 628 patients with advanced EC [30]. Pembrolizumab significantly improved median OS (9.3 months vs. 6.7 months; HR 0.69; 95% CI 0.52–0.93; P = 0.0074) and 12-month OS rates (43% vs. 20%) compared with chemotherapy in patients whose tumors had a PD-L1 CPS >10. Recently, nivolumab has been accepted as a second-line therapy for ESCC in Japan based on ATTRACTION-3 outcome [31]. A total of 419 previously treated patients with ESCC were randomly assigned to nivolumab (n = 210) and chemotherapy (n = 209). OS was significantly improved in nivolumab; median OS in the nivolumab and chemotherapy group was 10.9 months and 8.4 months, respectively (HR 0.77; 95% CI 0.62–0.96; P = 0.019) [32]. In the KEYNOTE-180 trial, 121 patients with EC (63 ESCC and 58 EAC) who progressed after two or more prior therapies were assessed. Pembrolizumab monotherapy showed that ORR was 14.3% (95% CI 6.7–25.4%) in patients with ESCC and 5.2% (95% CI 1.1–14.4%) in patients with EAC [32]. ORR was higher in patients with PD-L1-positive tumor (13.8% vs. 6.3%) [28]. These results demonstrated the efficacy and tolerability of pembrolizumab as a third-line or subsequent therapy option in patients with heavily pretreated ESSC with high PD-L1 expression. (Table 1: list of currently approved immune check point inhibitors).

CONCLUSIONS

Esophageal and gastric cancer remains a significant cause of all cancer-related deaths worldwide. With a spiked increase in incidence being observed in certain Western countries, 5-year survival rates have been shown at rates of 10–15%. Most patients have already manifested advanced disease at diagnosis and are therefore precluded from curative surgical resection.

Esophageal and gastric cancer is challenging to treat and requires a multidisciplinary approach to improve outcomes. The management of these diseases in the advanced setting has advanced the use of immune checkpoint inhibitors. The future challenge is to identify molecular targets based on tumor profiling. The results of further and ongoing clinical trials will contribute to establishing the most appropriate interdisciplinary strategy for each stage of each histologic subtype.

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Corresponding author:

Dr. Amptoulach Sousana,
Division of Oncology, Department of Medicine,
University Hospital of Patras, Patras, Greece, PC 26504
Tel. +30 2610999535, E-mail: drsouzana@yahoo.gr

New Oral Anticoagulants for the prevention of thromboembolic events in patients with Atrial Fibrillation

Christoforos Travlos[1], Georgios Leventopoulos[2]

Abstract

The choice of an OAC (oral anticoagulant) for patients with non-valvular atrial fibrillation (NVAF) is a very complex process. For many years the gold standard in the treatment of these patients was vitamin K antagonists (VKA), primarily warfarin. However**,** achieving well controlled therapy with warfarin is a very demanding process due to its narrow therapeutic range and its multiple drug and food interactions. Hopefully, over the last decade, new oral anticoagulants (NOACs) have emerged and constitute an alternative to warfarin. Current data suggest that NOACs are at least as effective and safe as warfarin for most NVAF subjects. In this article we try to delineate current knowledge concerning the use of NOACs in the prevention of thromboembolic events in patients with atrial fibrillation (AF).

Key words: *Atrial fibrillation; anticoagulation; NOACs*

INTRODUCTION

Atrial fibrillation (AF) is associated with an increased risk of morbidity and mortality, as a result of the high stroke risk in this population [1,2], which is five times higher compared to the general population [1]. Most of these strokes are disabling. Under these circumstances, it is imperative for most AF patients to be on lifelong anticoagulation treatment [2]. Vitamin K antagonists, such as warfarin and acenocoumarol, have been proposed [3]. Warfarin therapy can be very effective in the prevention of stroke in patients with AF reducing by 64% the relative risk compared to control / placebo and by 26% all-cause mortality. The Achilles' heel of warfarin is the labile international normalized ratio (INR). Keeping stable INR values is not simple for most patients [4,5]. This is attributed mainly to the narrow therapeutic range of warfarin defined as an INR of 2.0–3.0. It has been shown that the beneficial effect of warfarin is highly correlated to the time interval during which the INR lies within the therapeutic range (TTR) that should be >70% [6]. Otherwise, an elevated INR increases bleeding risk, whereas a low INR leads to more stroke events [7,8].

Moreover, warfarin levels depend on food and drug interactions which vary amongst individuals. As a result, it is difficult for patients and healthcare providers to find the right dose that maintains INR within the aforementioned range [4,5]. A failure to achieve TTR can be predicted by the multiple common risk factors that have been defined and prospectively validated [6]. Bleeding risk during warfarin treatment is one of the most important concerns of both physicians and patients, because major bleeding events are associated with increased morbidity and mortality [5,7].

A solution to these issues has been given by the introduction of new oral anticoagulants (NOACs). Routine coagulation monitoring is obsolete as daily dose is fixed. This offers convenience without compromis-

[1]Faculty of Medicine, University of Patras, Patras, Greece
[2]Department of Cardiology, University General Hospital of Patras, Patras, Greece
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ing effectiveness [8]. Moreover, their pharmacokinetic (PK) – pharmacodynamic (PD) profile is consistent [9]. The category of NOACs includes four drugs, of which, dabigatran was the first approved from the FDA in 2010. Dabigatran is a direct thrombin inhibitor. Rivaroxaban, apixaban, and edoxaban fall under the category of direct factor Xa inhibitors that were approved in 2011, 2014, and 2015, respectively.

The aim of this review is to provide an overview of existing clinical trial data on the use of NOACs about the prevention of thromboembolic events in patients with AF and to provide a summary on existing data regarding the treatment of special subpopulations.

The phase III NOAC trials

Four main NOAC trials (the RE-LY (dabigatran 150 mg or 110 mg vs warfarin) [10], ROCKET AF (rivaroxaban vs warfarin) [11], ARISTOTLE (apixaban vs warfarin) [12], and ENGAGE AF–TIMI 48 (edoxaban 60mg or 30 mg vs warfarin) [13] have been conducted in the context of the management of AF. All these major trials convey the same clinical message. Now more drugs are available in our armory that are at least not inferior to warfarin in terms of safety (bleeding) and efficacy (prevention of stroke and systemic embolism) [10–14]. Although these trials have many similarities, there are some important differences in trial design, study participants and outcome measures that should be considered, and have been analyzed by numerous reviews [15–17].

In these four trials, 42.411 participants received a NOAC and 29.272 participants received warfarin. Results from a meta-analysis [14] showed that stroke and systemic embolism were significantly reduced in patients receiving NOACs. This result was mainly due to the substantial protection against hemorrhagic stroke, which was reduced by half. Hemorrhagic stroke is the most devastating complication of anticoagulant treatment. Its reduced incidence during NOAC treatment is highlighted as the most important advantage over warfarin. In terms of ischemic stroke prevention, the NOACs were similarly effective to warfarin, which itself is very effective in this regard and reduced ischemic stroke by two-thirds compared with placebo [18]. In general, the NOACs safety profile was favorable compared with warfarin. Results from the same meta-analysis, showed that patients who received a high dose of NOAC (150 mg for dabigatran, 60 mg for edoxaban and the standard dose for apixaban and rivaroxaban) had a 14% non-significant reduction in major bleeding [14]. NOACs were, however, associated with increased gastrointestinal (GI) bleeding except for apixaban that was shown to cause less GI bleeding compared to warfarin in the ARISTOTLE trial. Apixaban was also associated with a marginally statistically significant reduction in all-cause mortality compared with warfarin.

Differences between study populations

In all four trials [10–13] the enrolment of the patients was based on their $CHADS_2$ score. During the enrollment phase, $CHADS_2$ score was not yet replaced by the more updated CHA_2DS_2VASc score. However, it is worth mentioning that the RE-LY [10] and ARISTOTLE [12] trials enrolled patients with AF $CHADS_2$ risk of 1 (i.e., low-risk patients), while the ROCKET-AF [11] and ENGAGE AF-TIMI 48 [13] trials required patients to have two or more risk factors for stroke (moderate- and high-risk patients) [19]. Thus, there is more experience in higher risk patients with rivaroxaban or edoxaban. On the other hand, patient enrolled in RELY and ARISTOTLE had less comorbidities and hence lower CHADS2.

The risk of stroke was higher in patients enrolled in ROCKET-AF (3.5 mean $CHADS_2$ score) than in patients enrolled in the other three trials (2.1, 2.2, and 2.8 mean $CHADS_2$ score in RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48 trials, respectively). In the ENGAGE AF-TIMI 48 trial, 52% of patients had a $CHADS_2$ score of < 3. In the ROCKET-AF and ENGAGE AF-TIMI 48 trials no patients with a $CHADS_2$ score of 0 or 1 where included, whereas the RE-LY and ARISTOTLE trials enrolled 32 and 34% of the patients in this low-risk category, respectively. As a consequence, the ROCKET-AF and ENGAGE AF-TIMI 48 trials had higher percentages of patients with hypertension, diabetes, and congestive heart failure. Moreover, in the ROCKET-AF trial 55% of the patients had a history of stroke or transient ischemic attack, whereas this proportion was <30% in each of the other three trials. The percentage of patients with paroxysmal AF was higher in the RE-LY trial (33%) and the ENGAGE AF-TIMI 48 trial (25%) compared to the other trials (Table 1).

NOACs vs NOACs

There are no head-to-head clinical trials comparing the efficacy of NOACs versus other NOACs. However, it has been shown by indirect comparisons and network meta-analyses based on randomized clinical trials (RCTs) that NOACs have generally similar efficacy but varied safety profiles [20,21]. Both the effectiveness and safety of NOACs have been evaluated by emerging observational studies in US clinical practice using single data

Table 1. *CHADS2 score of the participants in the four trials.*

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48
CHADS2 score	2.1 (mean)	3.5 (mean) / 3.0 (median)	2.1 (mean)	2.8 (mean)
CHADS2 score 0–1 (%)	33	0	34	0
CHADS2 score 2 (%)	34	13	36	48
CHADS2 score 3 -6 (%)	33	87	30	52

sources. They provide some evidence of the comparative effectiveness and safety between NOACs but with limited generalizability and a lack of a comprehensive evaluation on outcomes across various subgroups within NVAF patients [22,23].

THE ARISTOPHANES study (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients) compared the rates of stroke/systemic embolism and major bleeding [24]. Additionally, it evaluated comparative rates across various subgroups among NVAF patients newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin.

According to this study the unadjusted incidence rate of stroke/systemic embolism, including ischemic stroke, hemorrhagic stroke, and systemic embolism, was 1.3 (apixaban), 1.4 (dabigatran), 1.4 (rivaroxaban), and 2.1 (warfarin) per 100 person-years. The unadjusted incidence rate of major bleeding was 3.6 (apixaban), 3.6 (dabigatran), 5.4 (rivaroxaban), and 6.3 (warfarin) per 100 person-years.

Eligibility of NOACs

NOACs are approved for stroke prevention in 'non-valvular' AF [25]. The eligibility in most SmPCs (summary of product characteristics) is based on the $CHADS_2$ score given that it was commonly used in the phase III randomized clinical trials. The fact that they have consistent efficacy and safety, has led to the subsequent broadening of their indications on patients qualifying for anticoagulation according to the CHA_2DS_2-VASc score, with some regional differences (e.g., Canada, Japan).

Selected indications and contraindications, according to the European Society of Cardiology (ESC) guidelines [26], for NOAC therapy in AF patients are presented in Table 2.

NOACs and CAD

The coexistence of AF and coronary artery disease (CAD) apart from a common clinical scenario necessitates the combination of anticoagulation with antiplatelet treatment. According to the 2020 ESC guidelines

Table 2. *Selected indications and contraindications for NOAC therapy in AF patients.*

Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs VKA
Other mild to moderate valvular disease	Included in NOAC trials	Data regarding efficacy and safety overall consistent with patients without valvular heart disease
Bioprosthetic valve/valve repair (after > 3 moths postoperative)	Acceptable	Some data from NOAC RCTs
Severe aortic stenosis	Limited data	
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with antiplatelet treatment
Percutaneous tranluminar aortic vavluloplasty	With caution	No prospective data. May require combination with antiplatelet treatment
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs VKA Observational data positive for NOACs

[26], AF patients with co-morbid CAD have at least a CHA_2DS_2-VASc score of 1 (and most of the times even higher due to the presence of concomitant cardiovascular risk factors) and hence an absolute indication for oral anticoagulant therapy. It is well established that patients without AF need to be on dual antiplatelet treatment (DAPT) (i.e. aspirin and a P2Y12 inhibitor) for the prevention of stent thrombosis or recurrent events after an acute coronary syndrome (ACS) and/or stenting for CAD. DAPT is not sufficient for stroke prevention in case of AF and vice versa. NOAC as stand-alone therapy is not recommended in the immediate phase after ACS or coronary stenting. Therefore, the physician confronts a clinical dilemma about the choice of antithrombotic drug combination: undertreatment and increased risk for a coronary event and/or stroke, or overtreatment and increased risk for a bleeding event.

The combination of NOACs with antiplatelet agents (dual antithrombotic therapy) in patients with AF and ACS or patients who have undergone PCI, in comparison with warfarin combined with a P2Y12 inhibitor and aspirin (triple antithrombotic therapy) exceeds the purpose of this review. However, data from other four trials (RE-DUAL PCI [27], AUGUSTUS [28], PIONEER AF-PCI [29], ENTRUST-AF PCI [30]) that were mainly designed to compare the safety (bleeding events) and not the efficacy (prevention of thromboembolic events), show the superiority of dual (NOAC + P_2Y_{12} inhibitor) vs triple (warfarin + P_2Y_{12} inhibitor + aspirin) antithrombotic therapy.

In figure 1 we present the latest ESC guidelines concerning anticoagulation therapy after elective PCI or ACS in patients with AF.

NOACS PATIENTS' SUBGROUPS

NOACs in older populations

A significant proportion of older people (>75 years) has been included in all initial major trials and subsequent studies, ranging from 31% to 43%. They comprised over 27.000 elderly patients in whom NOACs were studied. As in the general population, NOAC treatment in older patients similarly reduced stroke rates compared to VKA. More importantly, a higher absolute risk was noted compared to younger patients, resulting in a lower number needed to treat [31–33]. Intracranial bleeding remains lower with all NOACs compared to VKA, but a significant age interaction was observed in older patients on the 150 mg dabigatran dose in terms of extracranial bleeding [34]. However, there was no relation between age and rates of extracranial major bleeding with apixaban, edoxaban or rivaroxaban compared to the overall trial results. Additionally, apixaban and edoxaban appeared to have lower major bleeding complications compared to VKA even in older age groups [32]. The risk of bleeding with age appears largely consistent with trial findings to date as it is indicated by observational registries in older cohorts [23, 34-37].

NOACs in patients with chronic kidney disease

Chronic kidney disease (CKD) and AF strongly interact with each other and are frequent comorbidities. The

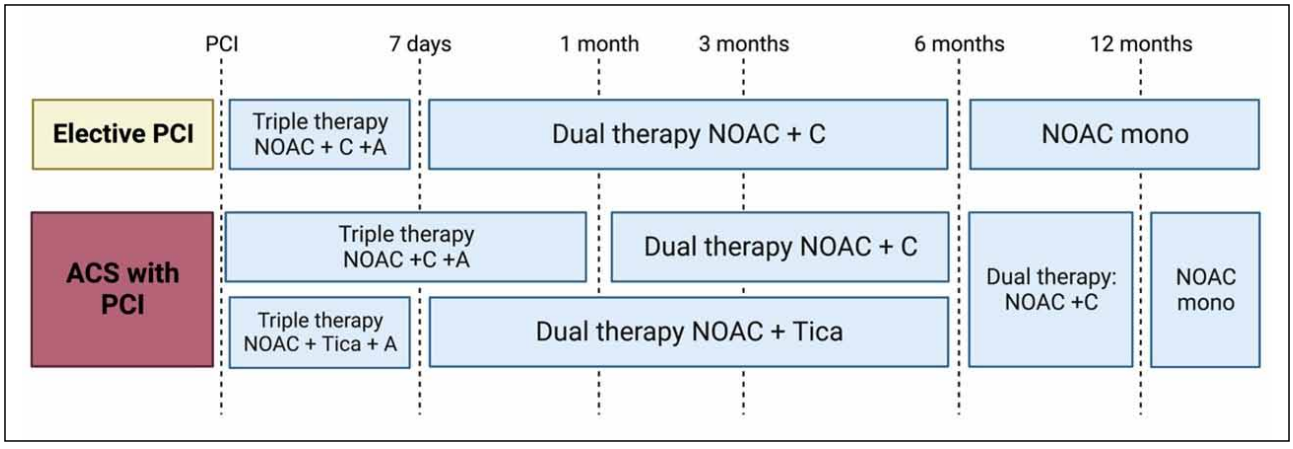

Figure 1. Anticoagulation therapy after elective PCI or ACS in patients with AF. Created with BioRender.com

Abbreviations: ACS: acute coronary syndrome, A: aspirin, C: clopidogrel, Tica: Ticagrelor, NOAC novel oral anticoagulant, PCI percutaneous coronary intervention.

Note: The duration of the triple antithrombotic therapy can be extended if the patient has high thrombotic risk i.e. left main PCI, proximal left anterior descending artery lesion, complex lesion, bifurcation lesion, recurrent myocardial infarction, stent thrombosis.

onset of atrial fibrillation promotes the progression of CKD and vice versa the establishment of renal dysfunction predisposes to AF [38–41]. Clinical management and risk stratification of patients with AF and CKD is very demanding as these patients carry both excessive thromboembolic and bleeding risk [42]. Pharmacokinetic properties differ among all four available NOACs and are mainly determined by kidney elimination: dabigatran has the greatest percentage of renal elimination (80%), compared to 50%, 35%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively.

Oral anticoagulant therapy in patients with severe CKD (CrCl of 15–29 mL/min)

Severe CKD -creatinine clearance (CrCl) of <30 mL/min – was an exclusion criterion in all landmark studies. A very small percentage of patients were studied on apixaban in the ARISTOTLE trial as the cutoff value was 25 ml/min. The small number of patients enrolled with CrCl 25-30ml/min is not sufficient for the generation of robust data. The current status is that patients with CrCl less than 15ml/h or on dialysis should be on warfarin [43]. Existing data on NOAC use is still weak in the aforementioned group. Another "grey" zone is the group of patients with ClCr 15-30ml/min. A reduced dose regimen of rivaroxaban, apixaban, and edoxaban (but not dabigatran) is approved in Europe for patients with severe CKD (stage 4, i.e. a CrCl of 15–29 mL/min). Dabigatran should not be given if ClCr is less than 30 ml/min due to its higher renal elimination compared to the other three NOACs. All three FXa inhibitors appear to have a favorable efficacy and safety profile compared to VKA in patients with severe renal dysfunction, as indicated by observational data that should be interpreted cautiously as there might be substantial confounding factors [44–46]. The 2020 ESC guidelines recommend the "cautious" use of factor Xa inhibitors at reduced doses for patients with CrCl 15–29 mL/min [26].

Oral anticoagulant therapy in patients with end-stage CKD (CrCl of 15 mL/min and/or dialysis)

In patients with end-stage renal dysfunction and on dialysis, the efficacy and safety of NOACs is unclear and more trials are needed. Till then, a case based individualized approach is followed regarding the dilemma to anticoagulate or not and (if so) which regimen to choose.

NOACs and cardioversion

According to the current ESC guidelines [26] NOACs are recommended with at least similar efficacy and safety as VKA in patients with NVAF undergoing cardioversion (CV) (Class IA). Prompt administration of NOACs or heparin is strongly recommended before CV (Class IIA). Furthermore, in OAC-naive patients with AF of ≥48 h (or unknown) duration, ESC guidelines [26] and the European Heart Rhythm Association (EHRA) consensus document [25] advocate two types of strategy: an "aggressive" early imaging-guided strategy followed by cardioversion or a "defensive" delayed non-imaging-guided strategy after regular and continued NOAC intake for at least 3 weeks before CV [47]. A recent modification is that there is a sub-classification of the first 48 hours to <12 hours and 12-48 hours. It is suggested to consider a more conservative approach in patients with AF presentation 12-48 hours and high CHA_2DS_2VASc score.

When the early strategy is chosen, a standard initial NOAC dose (rivaroxaban 20/15 mg, edoxaban 60/30 mg, dabigatran 150/110 mg) must be administered >4 h before cardioversion (≥2h after apixaban loading dose) and a TEE or a CT imaging is provisional to exclude left atrial appendage thrombus (LAAT) [48–50]. The EMANATE trial provided data that an initial loading dose of 10mg of apixaban (5 mg if does-adjustment criteria are applied) should be administered. Regarding the other NOACs, a loading dose is not recommended [25].

If a LAAT is found, cardioversion must be postponed for after a longer period of anticoagulation and after a repeated imaging test to confirm thrombus resolution. The best therapeutic strategy in this setting has not yet been established. But there are the possibilities of 1. converting to heparin to VKA or 2. start or continue with NOACs (best data with rivaroxaban and apixaban) especially in patients on VKA with poor anticoagulation quality (low time in therapeutic range).

On the contrary, limited data are available on safety and efficacy of NOACs for OAC-naïve patients with NVAF of <48 h duration. These patients are usually cardioverted without TEE after a single dose of low molecular weight heparin (LMWH). The last consensus document of EHRA on NOACs in NVAF recommends that these patients follow the local protocol with heparin/VKA as a first choice. As an alternative strategy we could use a single dose of NOACs or a loading dose of apixaban 2-4 h before CV to replace LMWH, according to patient thromboembolic risk and AF duration, with or without TEE [51].

However, there is no NOAC study on the peri-cardioversion setting including the EMANATE trial (the only

study to enroll a certain number of OAC-naive patients with AF of <48 h duration) to demonstrate non-inferiority in terms of safety and efficacy of a single dose of NOACs or a single loading dose of apixaban compared to LMWH in this clinical scenario [50].

The post-CV duration of anticoagulation with NOACs as for VKA depends on individual patient's thromboembolic risk assessed with CHA_2DS_2-VASc score. Long-term OAC therapy regardless of cardioversion success is required for men and women with a CHA_2DS_2-VASc ≥ 1 and ≥2, respectively. For patients with AF duration >48h and CHA_2DS_2-VASc score 0 in men and 1 in women, OAC therapy needs to be continued for 4 weeks post-CV. In contrast, the optimal duration of anticoagulation in AF ≤48h (especially when <12h) is unknown. In conclusion, anticoagulation with NOACs appears to be effective and safe in the peri-cardioversion setting [52].

Management of bleeding under NOAC therapy

NOACs are associated with lower rates of major and fatal bleeding events compared with warfarin as mentioned above. But clinicians may need to achieve rapid reversal of anticoagulation effects of the NOACs in an emergency setting. In Europe, idarucizumab – the direct antidote of dabigatran - is commercially available as opposed to andexanet alfa – the FXa antidote. However, both NOAC reversal agents are currently available in the US [53].

Peri-operative management of NOACs

The perioperative management of patients depends on the bleeding profile of the operation and the thrombotic risk as it is reflected by the CHA_2DS_2-VASc score. The advantageous management of NOACs is secondary to their faster onset and offset. NOACs should be preoperatively paused for operation with a high chance of bleeding risk. The time duration of pause is determined by two factors: the peri-operative bleeding possibility and the renal function of the patient. The pre-operative cessation should be prolonged up to 12h if the patient has been administered medications that increase the half-life of NOACs [54, 55]. NOACs do not require bridging with heparin. Only when the risk of peri-operative bleeding is substantially lower and gastrointestinal passage is back to normal, NOAC therapy can be resumed. For procedures with low bleeding risk, NOAC is reestablished within 6-8 h and the farthest being 24 h post-operation [54–56]. But for operations with a high risk of bleeding, NOACs are restarted within 48-72 h post-operatively [54].

Administration of antidote is considered in case of an emergency surgery with high bleeding risk. Before the administration of an antidote, the plasma level of the drug should be calculated in order to assess the level of coagulation [57,58]. Idarucizumab is administered intravenously at a 2.5-mg dose initially and then a maintenance dose within 15 min [57,58]. For factor Xa inhibitors, andexanet alpha acts by binding to the agents and eliminating them. In bleeding conditions, an IV bolus and a continuous intravenous infusion of the drug is administered for 120 min.

Under-dosing of NOACs

Patient characteristics, comorbidities, and physician judgment are some of the factors that contribute to current dosing patterns of NOACs**.** In clinical practice, under- or over-dosing of NOACs in patients with AF is not uncommon. The fact that under-dosing may be associated with reduced effectiveness for stroke prevention compared with the standard dose is shown by an analysis of prospective and retrospective registry and database studies on NOAC use in patients with AF (with at least 250 patients in each treatment arm] [59].

At this point we should mention that under-dosing regarding dabigatran is debated, because the RE-LY trial was the only one proving that the lower dosage (110mg) was not inferior to warfarin. The United States-based ORBIT-AF II registry found that 12.9% of patients received no recommended NOAC doses according to drug labeling, with 9.4% being under-dosed. Increased rates of hospitalization for cardiovascular reasons were seen in under-dosed patients compared with patients receiving the recommended dose. The highest rates of under-dosing occurred in patients receiving apixaban (12% of the overall population), particularly those on dialysis (29%; according to the U.S. label, patients on dialysis, aged <80 years, and with a body weight >60 kg, can be treated with apixaban 5 mg bid if indicated), and in those with an estimated CrCl of 30–50 mL/min receiving dabigatran (23%) [60].

The Greece-based PAVE-AF antithrombotic study in older patients with atrial fibrillation showed that 63.2% of patients received NOAC dosing consistent with European label recommendations, 29.7% received a lower dose, while 7.1% were overdosed. The highest rates of under-dosing occurred in this study in patients receiving apixaban (38.5% of the overall population treated with apixaban] [61].

Table 3. *Dose adjustment for NOACs according to chronic kidney disease severity.*

	GFR (mL/min) estimated using the Cockcroft-Gault equation			
Recommended oral anticoagulant	≥50	30 –49	15–29	<15
Dabigatran	150 mg twice daily 110 mg twice daily ≥80 years, or high risk of hemorrhage		The United States (based only on FDA approval) - 75 mg twice daily Europe - NO	No
Rivaroxaban	20 mg once daily	15 mg once daily (dose used by landmark trials)		No
Apixaban	5 mg twice daily 2.5 mg twice daily if any ≥2 of the following: age ≥ 80 years, body weight ≤ 60 kg and creatinine ≥1.5 mg/dL		2.5 mg twice daily	The United States – **5 mg twice daily** Europe - NO

Dose adjustment for NOACs according to chronic kidney disease severity

We present the recommended dose of NOACs according to chronic kidney disease severity in patients with AF in Table 3. Dosage recommendations are derived from the analysis of data in the subgroups with AF and renal dysfunction from the landmark trials (dabigatran-RE-LY, rivaroxaban-ROCKET-AF, apixaban-ARISTOTLE). It is very important to mention that patients with GFR < 30 mL/min (<25 mL/min for apixaban) were excluded from these trials.

The dose of 15 mg for rivaroxaban is recommended if GFR is between 15-49 mL/min and dabigatran 150/110 mg is recommended if GFR is more than 30 mL/min. For apixaban if 2 out of 3 conditions are met (age ≥ 80 years, body weight ≤ 60 kg and creatinine ≥1.5 mg/dL) then the dose is reduced to 2.5 mg BID. This rule was applied in the ARISTOTLE trial where GFR < 25 mL/min was an exclusion criterion. Thus, in practice it applies when GFR is more than 30 mL/min since a very low number of patients were enrolled with GFR of 25-30 mL/min. If someone has GFR < 15-30 mL/min the rule is not valid, and these patients should take the reduced dose 2.5 BID [29].

CONCLUSIONS

NOACs are at least non-inferior to VKAs in the prevention of stroke and systemic embolism in patients with NVAF and they provide the benefits of rapid onset and offset, no pharmacodynamic monitoring or diet restrictions, fewer drug interactions, and predictable pharmacodynamics. Also, NOACs are associated with decreased rates of major bleeding, intracranial and fatal bleeding. New oral anticoagulants offer a reasonable option for patients undergoing cardioversion and facilitate access to surgical procedures. However, the relative safety and efficacy of NOACs in certain patient sub-populations (e.g., older populations and patients with chronic kidney disease) is not well established. Specific antidotes such as andexanet alfa (for Xa inhibitors) and idarucizumab (for dabigatran) can improve outcomes of bleeding or emergency surgery.

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Corresponding author:

Georgios Leventopoulos, Electrophysiologist, Consultant, Department of Cardiology, University General Hospital of Patras, Patras, Greece. Pineiou 33, 26442, Patras
Tel.: +30 6977 786020, Fax: 2613603281
e-mail: Levent2669@hotmail.com

Staging of Chronic Kidney Disease (CKD) and principles of CKD management

Lamprini Balta[1,2]

Abstract

Chronic Kidney Disease (CKD) is a multistage condition accompanied by a wide variety of health implications impairing patients' quality of life and adding to the financial burden of health-care systems. Diabetes mellitus (DM) and hypertension are the main causes of CKD, thus special care is required to ensure that they are properly managed. Advances in patient classification enable clinicians to early recognize those at risk and aid the process of decision-making. CKD is classified into 5 stages according to the estimated glomerular filtration rate (eGFR) and into 3 stages according to albuminuria. Notably, CKD progression is neither given nor linear, since only a minority of patients develops stage 5 CKD. Although, patients should be carefully evaluated during every stage, evidence suggest that stage 3b acts as a crucial threshold where several issues must be promptly addressed in order to mitigate the risk for kidney function deterioration and cardiovascular events. Overall, the prerequisites for achieving optimal outcomes for CKD patients include the willingness of patients to adopt the appropriate lifestyle changes and the commitment of clinicians to diligently and collaboratively deal with the challenges rising in every step of the disease.

Key words: *Chronic kidney disease; proteinuria; estimated glomerular filtration rate*

INTRODUCTION

Chronic Kidney Disease (CKD) is most common among people over 70 years old. People with CKD are 16-40 times more likely to die from other causes before they reach end-stage CKD (ESCKD). Patients with CKD have significantly higher rates of morbidity, mortality, hospitalization, and healthcare utilization [1]. The prevalence of CKD in the general adult population worldwide is 11-13% [2]. The prevalence of CKD stages 2–5 continues to rise since 1988. Diabetes mellitus (DM) and hypertension account for approximately 40% and 25% of CKD cases, respectively, while they are responsible for the majority of ESCKD cases. Meanwhile, these diseases are expected to increase in the future thus augmenting the burden for healthcare [3]. Early diagnosis and monitoring can prevent kidney disease progression. Patients with CKD can be classified depending on their level of kidney function, or eGFR, and the amount of protein present in urine. This information forms the basis of CKD staging and helps to risk stratify patients. The higher the stage (G1→G5) and the greater the amount of protein present in urine (A1→A3), the more "severe" the CKD. Optimal management of patients with CKD requires appropriate interpretation and use of the markers and stages of CKD, early disease recognition, and close collaboration between primary care physicians and nephrologists.

CKD definition

CKD is defined as abnormalities in kidney function (estimated glomerular filtration rate (eGFR)< 60 ml/min/1,73m^2) or structure, present for more than three months, with implications for health. Markers of kidney disease may include the following:

[1]Department of Nephrology and Kidney Transplantation, University Hospital of Patras, Patras, Greece.
[2]General Hospital of Preveza
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- albuminuria: albumin to creatinine ratio (ACR) > 30mg/g
- hematuria: microscopic hematuria or red-blood cell casts
  - renal histological abnormalities
- electrolyte disorders (due to tubular disorders)
- structural abnormalities (polycystic kidney disease, reflux nephropathy, small kidney size, medullary sponge kidney)
  - history of kidney transplantation

CKD staging

CKD is classified based on eGFR and the level of proteinuria. CKD staging helps planning patients' follow-up and management. The traditional 5 stages of CKD (Table 1) rely solely on eGFR and were adopted up to 2002 [4]. However, according to the latest KDIGO (The Kidney Disease: Improving Global Outcomes) 2012 Clinical Practice Guidelines for the evaluation and management of CKD, patients are classified as G1- G5 (Table 2), based on eGFR, and A1-A3 (Table 3) based on the ACR [5]. This change was primarily introduced to indicate the increase in cardiovascular risk and risk of further progression associated with stage 3b as demonstrated by several clinical studies [6,7]. It is important to note that patients with eGFR of >60 ml/min/1.73m^2 should not be classified as having CKD unless they have other markers of kidney disease [8]. eGFR is primarily. determined by serum creatinine (SCr), and the preferred method for estimating GFR is the CKD-Epidemiology Collaboration (CKD-EPI) Equation [9] based on SCr, age, gender, and ethnicity according to the following formula:

$$eGFR = 141 * \min(SCr/\kappa,1)^{\alpha} * \max(SCr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018 \text{ [if female]} * 1.159 \text{ [if black]}$$

Proteinuria

ACR (or PCR) measurements are usually performed on a random urine sample preferably the first morning sample. ACR is more sensitive to detect low levels of proteinuria and is the recommended method for screening and measuring proteinuria in patients with DM. For the quantification and monitoring of higher levels of proteinuria (eg, ACR > 700 mg/g), PCR or albumin measurement in a 24-hour urine collection is preferred. A PCR of 1000 mg/g, or ACR of 700 mg/g, is approximately equal to 1 g of protein per 24 hours.

Patients with proteinuria are at increased risk of developing cardiovascular disease (CVD), in addition to progressive kidney disease [10]. Therefore, strategies should be employed to re duce the cardiovascular risk for these patients such as: smoking cessation, physical exercise, reduce body weight to optimal goals and antilipidemic therapy [11]. Regarding antilipidemic therapy, the following instructions should be followed:

- In adults over 50 years and eGFR ≥ 60 ml / min / 1.73m2, initiate statin treatment
- In adults over 50 years and eGFR < 60 ml / min / 1.73m2, initiate statin or statin/ezetimibe combination
- In adults under 50 years, with a known history of CVD, Myocardial Infarction, DM or Systematic Lupus Erythematosous (SLE), initiate statin treatment

Randomized trials on proteinuria-lowering treatment emphasize the importance of intervention in slowing CKD progression and reducing the development of cardiovascular events.

Antihypertensive agents that interfere with the renin angiotensin system (RAS), including angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs), have been consistently shown to reduce proteinuria and the rate of renal

Table 1. *NFK-K/DOQI Classification of Chronic Kidney Disease.*

Stages	GFR (mL/min/1.73m^2) ≥90 (with CKD risk factors)	Prevalence in US Population (millions) N/A	Action Screening, CKD risk reduction
1	≥ 90	5.9 (34.3%)	Diagnosis and treatment. Treatment of comorbid conditions: Slowing progression of CKD
2	60-90	5.3 (5.3%)	Estimating progression
3	30-59	7.6 (4.3%)	Evaluation and treating complications
4	15-29	0.4 (0.2%)	Preparation for kidney replacement therapy
5	< 15 (or dialysis)	0.3 (0.1%)	Replacement (if uremia present)

Table 2. *GFR categories in CKD.*

Grade	GFR (mL/min/1.73 m^2	Kidney function
1	≥90	Normal or high
2	60-89	Mildly decreased
3A	45-59	Mildly to moderately decreased
3B	30-44	Moderately to severely decreased
4	15-29	Severely decreased
5	< 15	Kidney failure

function deterioration in patients with diabetic and non-diabetic kidney disease, independently of blood pressure (BP).

It should be noted that in the background of DM, albuminuria is a crucial feature for the progression of CKD. As a general guideline, in diabetic patients, serum ACR and SCr should be measured at least annually followed by referral to a nephrologist when necessary. Moreover, the presence of albuminuria (ACR> 30 mg/g) is a strong indication for the initiation of RAS block therapy, aiming at a BP target of less than 130/80mmHg [12].

Blockade of the RAS is also recommended for adults with a urine ACR of at least 300 mg/ per 24 hours. Dual therapy with an ACE-I and an ARB is generally avoided, given the associated risks of hyperkalemia and acute kidney injury.

Recently, sodium-glucose cotransporter 2 inhibitors (SGLT2i) were introduced as a therapeutic choice for DM. Mechanistically, these agents function by blocking glucose entry into the renal proximal tubule cells, facilitated by the SGLT2 transporter, thus leading to enhanced urinary glucose excretion [13]. A number of studies in patients with type 2 diabetes (T2D) have demonstrated that SGLT2i display renoprotective effects in manners independent of its glucose-lowering effects [14,15]. It appears that SGLT2i cause reduction of renal hyperfiltration thus mitigating the subsequent albuminuria [16]. Moreover, their natriuretic effect causes a decrease in BP. Taken together, these data suggest that SGLT2i may have a place in standard therapy of CKD.

Management of CKD stages G1 and G2

Initial assessment for most of these patients should be undertaken in the context of primary healthcare. The major aim of this assessment is to determine which patients are at risk of developing progressive renal disease. For this reason, all patients should be subjected to ACR, SCr and BP measurements, while they should also undergo urine analysis to check for blood and/or protein. The necessity for BP measurement is well justified given the bidirectional connection between CKD and hypertension, since CKD can be a complication of hypertension while CKD (of any etiology) can be associated with hypertension. Special care should be given at patients displaying a high risk of developing end-stage renal disease (stage G5) as these patients should be referred to a nephrologist [17]. Indicators for the devel opment of kidney disease include proteinuria (in patients without diabetes if ACR> 300mg/g), hematuria of glomerular origin, rapidly deteriorating renal function, family history of renal failure, difficult-to-control hypertension.

Management of CKD stage G3

Patients falling in this stage should also be assessed by primary health-care practitioners. The goal here, also, is to determine which patients are at increased risk of developing kidney disease and should be referred to a nephrologist. Markers of renal disease progression are the same as described at stages G1 and G2.

The patient should be subjected to thorough clinical assessment and ultrasound imaging of kidney, bladder and prostate (if men), while an overview of prescribed medication should be performed (i.e., to exclude the use of nephrotoxic drugs). Additionally, a careful recording of personal history could reveal the

Table 3. *Albuminuria categories in CKD.*

Category	AER (mg/dl)	Approximately Equivalent ACR (mg/mmol) (mg/g)	Terms
A1	< 30	< 3 < 30	Normal to mildly increased
A2	30-299	3-29 30-299	Moderately increased
A3	≥ 300	>30 ≥300	Severely increased

presence of severe comorbidities (DM, hypertension, multiple myeloma, connective tissue disease) and family history of CKD.

Long-term monitoring of renal function, proteinuria and blood pressure should be performed, with the aim of identifying a minority of patients with stage CKD G3 who will progress to end- stage renal disease and the detection of CKD complications. Renal function should be monitored at least annually. For patients with significant proteinuria (i.e., A3) renal function should be checked at least twice yearly. A brief guide to abide by is the following:

- Anemia: Non-renal causes must be ruled out first. Significant anemia due to CKD is rare before the G3b stage. For patients with hemoglobin levels below 10.0 g/dL special interventions should be considered (iron administration, initiation of erythropoietin) [8].
  - Cardiovascular risk: smoking cessation, exercise, initiation of statin or statin/ezetimibe combination for primary and secondary prevention of CVD.
  - Immunization: against influenza virus and pneumococcus
  - Drug review: to minimize the exposure to nephrotoxic drugs (especially NSAIDs) and ensure that medication doses are appropriate for the level of kidney function [18]

Management of CKD stage G4 and G5

Patient monitoring at these stages must be performed by a specialist Nephrologist. Managing patients with G4 and G5 requires addressing several aspects of CKD. Efforts should focus on the need to slow down CKD progression while maintaining alertness in order to identify and treat possible CKD complications. Meanwhile, special care should be given to help reduce the incidence of CVD and to allow timely and informed decision-making regarding the management of ESCKD. Typically, patients should be assessed on a 1-2 monthly basis. Factors to be monitored and addressed include:

- Hyperkalemia: a diet low in potassium should be followed, manage medication- induced hyperkalemia [19].
  - Metabolic acidosis: Treatment with bicarbonate supplement aiming at HCO3 > 22mEq/L.
  - Anemia: exclusion of other causes of anemia. When Hb <10.0 g / dL, special interventions should be considered (iron administration, initiation of erythropoietin). The goal of treatment is to maintain Hb levels 11.5 g/dL.
  - Calcium and phosphate disorders: restriction of dietary phosphates, orally supply "activated" (1α-hydroxylated) vitamin D and phosphate-binding factors.
- Blood pressure: Target BP<130/80 mm Hg. A SBP target <120mmHg is suggested, if tolerated (KDIGO BP Guidelines 2021) [20].
- Cardiovascular risk: smoking cessation, exercise, initiation of statin **t**reatment or statin/ ezetimibe combination for primary and secondary CVD prevention [21].
  - Fluid balance: salt and water retention are common in patients with impaired renal function. Deterioration of fluid retention may require the initiation or increase of diuretics and may accelerate the need to initiate renal replacement therapy.
  - Immunization: Influenza and pneumococcal vaccinations should be given. Patients who may need renal replacement therapy should be vaccinated against hepatitis B.
  - Drug review: minimize exposure to nephrotoxic drugs (especially NSAIDs) and ensure that medication doses are appropriate for the level of kidney function. Metformin should be avoided in patients with CKD stage G4 and G5.

Patients in these stages should be educated about treatment options. Kidney transplanta tion is considered the optimal therapy for ESKD, with living donor kidney transplantations performed before or shortly after hemodialysis initiation. Alternative therapies for ESKD may include in-center hemodialysis and peritoneal dialysis. The KDIQO guidelines recommend that access creation should occur when eGFR is between 15 and 20 mL/min/1.73 m^2.

COMMENTS

- Stratification of CKD into 5 stages helps clinicians focus on CKD management aspects.
- Notably, the majority of CKD stage 3 or 4 patients will not develop CKD Stage 5 / kidney failure (~1% risk).
- Early examination and intervention in patients at risk for CKD are necessary because progressive CKD is associated with adverse clinical outcomes, including ESKD, CVD, and increased mortality.
- Appropriate clinical measures should be performed, to manage the risk and increase the safety of patients with CKD.
- Co-management and referral of patients to specialist

Nephrologists, when appropriate, in order to improve the results in CKD.

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Corresponding author:

Lamprini Balta
Seleukeias 2, Preveza, 48 100
Tel.: +30 2682361 221
e-mail: lianabalta@gmail.com

Chest pain and high-sensitivity troponin: Diagnostic utility

Athanasios Moulias, Theoni Theodoropoulou, Angeliki Papageorgiou, Grigorios Tsigkas, Periklis Davlouros

Abstract

Chest pain is one of the most common causes of emergency department (ED) visits worldwide. Early diagnosis in patients with suspected myocardial infarction (MI) is of paramount importance, in order to timely provide appropriate therapy and reduce the duration of stay in the ED. For this purpose, high sensitivity cardiac troponin (hs-cTn) assays have been developed and are used by thousands of physicians worldwide. Hs-cTn assays are latest generation tests that allow the detection of very low levels of circulating troponin within a short period of time. When used in the context of established algorithms, hs-cTn measurements reduce the time needed for the safe rule-in or rule-out of MI and, consequently, improve the management of patients presenting with suspected acute coronary syndrome (ACS). However, hs-cTn levels can be elevated in several other conditions associated with cardiomyocyte injury; therefore, the clinician should be aware of the caveats of using rapid rule-in/rule-out algorithms. This article presents the diagnostic utility of the hs-cTn assays and summarizes primary principles for their appropriate, safe and effective use in clinical practice.

Key words: *Chest pain; acute coronary syndrome; troponin; rapid rule-in; rapid rule-out*

INTRODUCTION

It is estimated that as many as 20 million patients present to emergency departments (ED) annually in North America and Europe with various symptoms that may be related to myocardial ischemia [1], such as chest discomfort, shortness of breath, nausea, vomiting, weakness and fatigue. None of these symptoms is specific for acute coronary syndrome (ACS) and, thus, diagnosis is often challenging [2]. In the majority of these patients, the final diagnosis is a noncardiac disorder, rather than ACS, such us pulmonary embolism, pleuritis, chest trauma, acute herpes zoster, rheumatoid arthritis, peptic ulcer or gastroesophageal reflux, etc. [3, 4] (Table 1). Until the development of hs-cTn, the application of a work-up in the ED including clinical assessment (risk factors, symptoms, vital signs), electrocardiogram (ECG) and cardiac biomarkers, resulted in missed MI and inappropriate discharge in ~2% of patients [2]. Missed MI is one of the most frequent malpractices in ED and has great medicolegal consequences. Recently, the use of hs-cTn has decreased this rate and has accelerated the rule-in/rule-out of ACS which is critical for the early initiation of therapy.

Diagnostics

The diagnostic evaluation of a patient presenting in the ED with chest pain (i.e., suspected ACS) should incorporate clinical presentation, physical examination, ECG and hs-cTn measurements in the context of established algorithms.

Clinical Presentation

Acute chest discomfort in ACS patients, usually

Department of Cardiology, General University Hospital of Patras, Patras 26504, Greece

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Table 1. *Differential diagnosis of acute chest pain [4]*

Cardiac	Pulmonary	Vascular	Gastro-intestinal	Orthopaedic	Other
Acute coronary syndrome	Palmonary embolism	Aortic dissection	Esophageal spasm	Musculoskeletal disorders	Anxiety/panic attack
(Myo)pericarditis	Pneumothorax	Aortic aneurysm	Esophagitis	Muscle injury	Herpes zoster
Acute heart failure	Pneumonia		Peptic ulcer	Chest trauma	Anemia
Severe aortic valve stenosis	Pleuritis		Gastritis	Costochondritis	
Takotsubo syndrome			Pancreatitis		
Tachyarrhythmias			Cholecystitis		

presents with retrosternal sensation of pain, squeezing pressure or tightness, that may radiate to the left side of the chest, arm, shoulder, neck, jaw, and/or epigastrium and is precipitated by exertion or stress. Clinical presentation may also include accompanying symptoms such as dyspnea, pallor, nausea, vomiting, diaphoresis, anxiety and syncope. Atypical presentations like isolated epigastric pain, isolated dyspnea or minimal chest pain (i.e.,"silent MI") are more common in older patients, women, diabetics and in patients with chronic renal disease or dementia [4,5].

Physical Examination

Physical examination may be helpful for the differential diagnosis of chest pain (Table 1) in patients with suspected ACS. Findings like heart murmurs, irregular pulse, jugular vein distention, blood pressure difference between upper and lower limbs or between arms and friction rub, may suggest an alternative diagnosis. Additionally, the physical examination may contribute to the distinction between non-coronary causes of chest pain (cardiac tamponade, pericarditis, myocarditis, aortic dissection) and extracardiac pathologies (pneumonia, esophageal perforation, biliary colic, acute pancreatitis) [4].

Electrocardiogram (ECG)

The 12-lead ECG at the ED is the first-line diagnostic tool for the evaluation of patients with suspected ACS and should be performed as soon as possible (within 10 min) of the patient's arrival. ECG may be normal in more than 30% of patients with Non-ST-segment elevation ACS (NSTE-ACS). However, it may show abnormalities such us ST-segment depression, transient ST-segment elevation or T-wave inversion [4]. Regarding patients with left bundle branch block (LBBB) and a high clinical suspicion of ongoing myocardial ischemia, they should be managed as patients with STEMI irrespective of the time of LBBB appearance [6]. However, hemodynamically stable patients presenting with acute chest discomfort and LBBB have only a slightly higher probability of having MI in comparison with patients without LBBB. Consequently, hs-cTn measurement has a crucial role in deciding whether to perform immediate coronary angiography or not [7].

Standard and High sensitivity cardiac troponin (hs-cTn)

Diagnosis based solely on clinical assessment and ECG seems to be insufficient for patients with suspected NSTE-ACS. Thus, the measurement of a biomarker of cardiomyocyte injury, preferably cTn T or I, is the cornerstone of early diagnosis of MI [4]. Troponins T and I are specific to the heart and are released in the circulation whenever cardiac myocyte damage develops [8].

Recently, the evolution of laboratory techniques has led to the development of new advanced assays, the hs-cTn tests. Hs-cTn tests have a variety of characteristics that differentiate them from the older/conventional troponin test [8]. Firstly, they can detect a much lower serum concentration of cTn with a minimum detection level of 0.005 ng/ml, compared with 0.01 ng/ml when using cTnT (released in 2005) [9]. Moreover, the time frame for the second measurement of hs-cTn can be considerably shortened, due to the rapid detection of any minor myocardial injury [10].

Hs-cTn assays have significant clinical implications compared with standard cTn assays. Most importantly, they have higher negative predictive value for MI and reduce the "troponin-blind" interval leading to earlier

diagnosis of MI. Moreover, they have resulted in a ~20% relative increase in the detection of Type I MI and a corresponding decrease in the diagnosis of unstable angina. High sensitivity tests quantify the amount of cardiomyocyte injury [11, 12]. Therefore, they should be interpreted as quantitative variables and not as a binary system (positive/negative). The higher the cTn blood concentration, the higher the probability of MI; elevations up to 3-fold the upper reference limit have only limited (50-60%) positive predictive value (PPV) for MI and may be associated with various conditions. Higher elevations beyond 5-fold the upper reference limit have high (>90%) PPV for acute type 1 MI [13, 14]. The clinician should be aware of the various conditions beyond MI that are commonly associated with an elevation of cTn. These include cardiac conditions such as heart failure, structural heart disease (e.g. aortic stenosis, left ventricular hypertrophy), tachyarrhythmias, hypertensive emergencies, myocarditis, takotsubo syndrome, cardiac contusion, pulmonary embolism, and non-cardiac conditions such as acute neurological events (stroke, subarachnoid hemorrhage), sepsis, etc. [4,12]. It is noteworthy to mention that patients with cTn elevations have a worse prognosis than those with normal levels of cTn, irrespective of the etiology of troponin rise [15].

False positive measurements may be observed in very rare circumstances, in the absence of cardiomyocyte injury. In these cases, heterophilic antibodies or troponin autoantibodies may be present. Thus, if there is inconsistency between clinical presentation and cTn levels, false positive assay results should be considered [16].

Troponin based strategies for rapid rule-in and rule-out of MI

The novel high sensitivity cTn tests have an important clinical advantage; due to their ability to reduce the time interval to the second cardiac troponin assessment, they allow for a rapid diagnosis of MI in the ED. Thus, rapid strategies for the early rule-in and rule-out of MI have been developed and validated in large multicenter studies [14, 17-19]. Two of these strategies, the 0h/1h algorithm (blood draw at 0h and 1h from patient presentation at the ED) and 0h/2h algorithm (blood draw at 0h and 2h), are recommended (Class I, Level of Evidence B) by the European Society of Cardiology (ESC) (Figure 1) [4].

Diagnostic studies validated these two triage algorithms for patients with acute chest pain and/or suspected MI, and defined optimal thresholds for rule-out and rule-in. Sensitivity and negative predictive value (NPV) for MI was found to be equal to 99% and specificity and PPV equal to 70%. The 0h/3h algorithm should be considered as an alternative (Class IIa, Level of Evidence B) [20, 21]. These three strategies (0h/1h, 0h/2h, 0h/3h) are based on the absolute change between two measurements of hs-cTn concentration in the blood. The larger the absolute change of cTn levels within 1h, 2h or 3h, the higher the probability of MI [22]. The cut-off concentrations for the 0h/1h and 0h/2h strategies are assay specific (Table 2) [4]. Clinicians should be aware of the specific assay used in the healthcare facility they are providing service, in order to use the proposed algorithms appropriately.

It is important to mention that these novel strategies detect only MI and not unstable angina (UA). The rapid rule-in/rule-out algorithms should always be used in combination with full clinical assessment and ECG, in order to identify patients at high risk, who are unsuitable for early discharge and need further monitoring. Additional imaging tests, such us echocardiography, stress testing, computed tomography angiography (CTCA) or invasive coronary angiography may be important for an accurate diagnosis. Furthermore, these strategies should only be performed after the exclusion of STEMI from the initial ECG, because these patients need immediate perfusion therapy and so the measurement of cTn is not necessary [4, 12].

0h/1h algorithm

If at presentation (0h) the hs-cTn levels are very low and chest pain onset (CPO) is over 3h, MI can be ruled out. Another occasion where MI can be ruled out is the combination of a low initial concentration of hs-cTn at presentation (0h) and the absence of a significant rise within 1h (No 1hΔ). In cases where the hs-cTn levels at presentation are high or when there is significant increase of hsTn value within the first hour (1hΔ), then the patient is ruled-in for MI [4] (Figure 1).

It is important to highlight that the turnaround time for hs-cTn, in other words the time interval from blood draw until measurements become available to the clinician, is about 1 hour. Therefore, the results from the hs-cTn measurements which are performed at 1 hour after ED presentation will be reported back at about 2 hours after the patient's arrival at the ED (1h+1h). Thus, the clinicians can make the decision for rule-in or rule-out about 2 to 3 hours after ED presentation [4].

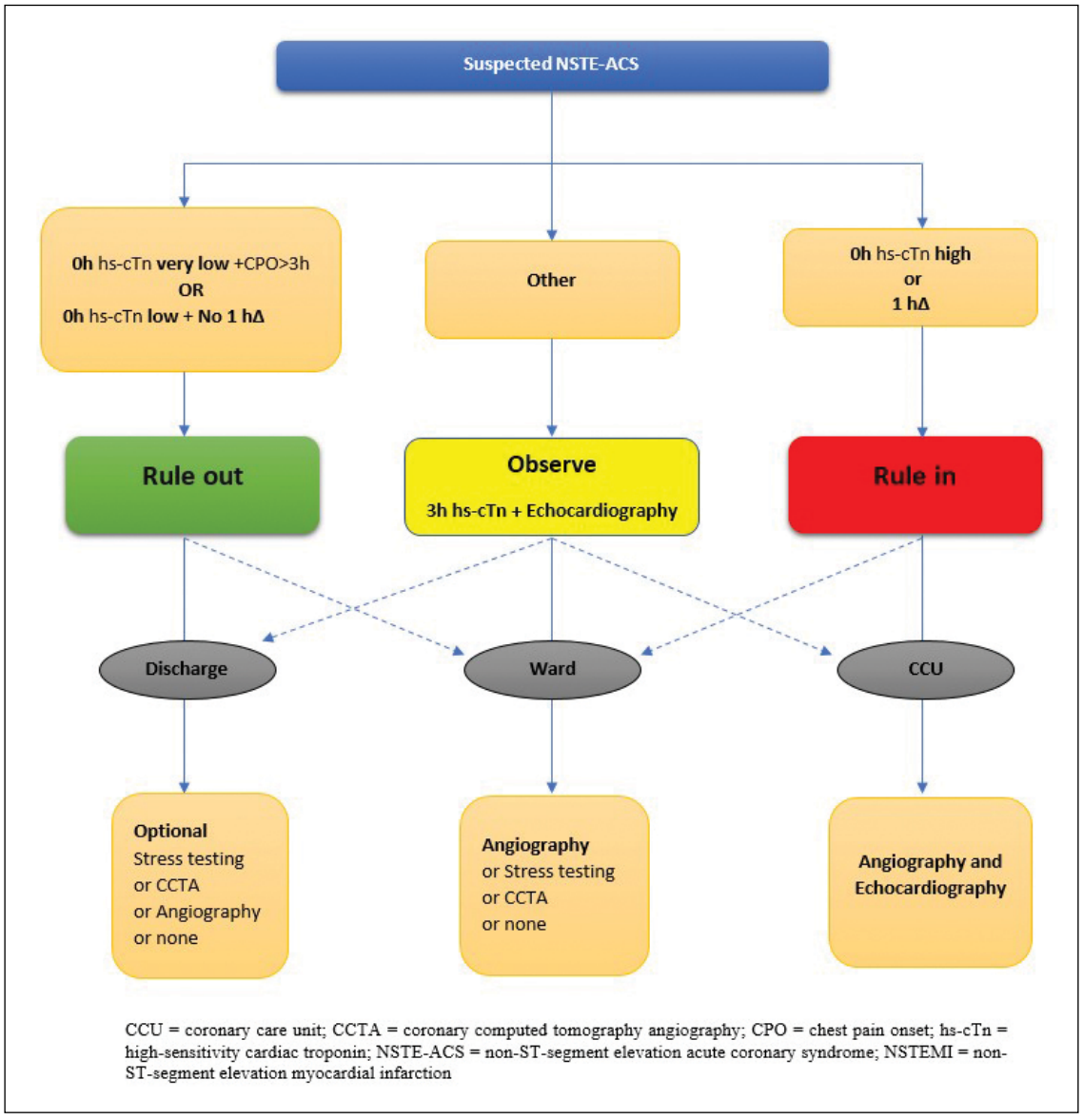

Figure 1. 0 h/1 h rule-out and rule-in algorithm using high-sensitivity cardiac troponin assays in patients presenting with suspected ACS at the emergency department [4].

0h/2h algorithm

The 0h/2h strategy measures concentration changes within 2 hours. Absence of significant 2hΔ, means that MI is ruled-out [4].

0h/3h algorithm

The recent ESC guidelines for NSTE-ACS recommend that the 0h/3h algorithm (a rapid rule-out and rule-in protocol with blood sampling at 0 h and 3 h) [23] should be considered as an alternative to the ESC 0h/1h algorithm, if a hs-cTn test with a validated 0 h/3 h algorithm is available [4].

However, evidence suggests that the ESC 0 h/3 h algorithm seems to balance efficacy and safety less well compared with the more rapid protocols (ESC 0h/1h, ESC 0h/2h) [20, 21]

0h/1h vs 0h/3h algorithm

The 0h/1h protocol is preferable in comparison with 0h/3h protocol, due to the fact that the first one allows to rule out more patients than the second one, without an increase in mortality [20]. It is noteworthy to mention that this algorithm has been validated in several multicenter studies and is distinguished for its high

Table 2. *Assay specific cut-off levels in ng/l within the 0 h/1 h and 0 h/2 h algorithms.*

0 h/1 h algorithm	Very low	Low	No 1hΔ	High	1hΔ
hs-cTn T (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTn I (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTn I (Centaur; Siemens)	<3	<6	<3	≥120	≥12
hs-cTn I (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
0 h/2 h algorithm	Very low	Low	No 2hΔ	High	2hΔ
hs-cTn T (Elecsys; Roche)	<5	<14	<4	≥52	≥10
hs-cTn I (Architect; Abbott)	<4	<6	<2	≥64	≥15
hs-cTn I (Centaur; Siemens)	<3	<8	<7	≥120	≥20
hs-cTn I (Access; Beckman Coulter)	<4	<5	<5	≥50	≥20

efficacy (PPV) and very high safety (NPV). Furthermore, it is simpler to perform, more rapid and is associated with fewer missed MI situations [4, 20].

Observe zone

Patients who cannot be assigned to the rule-out or rule-in zone, are assigned to the 'observe' zone. These patients constitute up to one third of those evaluated for suspected ACS and are usually men with pre-existing CAD and high long-term mortality [24]. Additional cardiac troponin measurement at 3 hours and echocardiography are the next steps, crucial for accurate diagnosis [24] (Figure 1).

Clinical assessment of mildly elevated cTn levels is integral, because up to one third of patients assigned to the observe zone will finally have a diagnosis of MI or UA. Thus, serial sampling of cardiac troponin at 3h is essential for the differential diagnosis between acute cardiac disease (MI) and chronic cardiac disease. MI is combined with a dynamic cardiac troponin course, while chronic cardiac disease is associated with a more stable hs-cTn elevation [25].

Patients with a high clinical suspicion of NSTE-ACS and a relevant change of cardiac troponin within 3 hours should undergo invasive coronary angiography, while patients with a low to intermediate suspicion of NSTE-ACS, should be offered noninvasive imaging tests (CCTA) after discharge, or imaging-based stress testing stress echocardiography, positron emission tomography, single-photon emission tomography (SPECT) or cardiovascular magnetic resonance imaging (CMR). In case of special conditions, e.g., rapid ventricular rate response to atrial fibrillation or hypertensive emergency no further diagnostic tests are recommended [4].

Patients with mild hs-cTn elevations

Mildly abnormal hs-cTn levels are just above the 99th percentile (up to 3 times the 99th percentile) and have a broad differential diagnosis [26]. The PPV for patients with acute chest discomfort and mild hs-cTn elevations is very low, about 50% [26]. Therefore, when clinicians are confronted with these challenging patients, they should first consider pre-test probability for MI based on clinical presentation (symptoms and signs) and ECG findings. Moreover, they should think about an obvious non-MI explanation for the mildly abnormal hs-cTn levels, such as acute tachyarrhythmia, acute pulmonary embolism or acute heart failure. They should also consider which diagnostic tests can be useful, such as a repetition of cTn measurement within 1 hour, echocardiography or CMR. Finally, a serious aspect that has to be mentioned, is that hs-cTn elevations, regardless of the cause, are associated with increased mortality. So, further examinations are important [26].

Confounders of cardiac troponin concentration

In patients presenting at the ED with suspected NSTE-ACS, besides the presence or absence of MI, there are four clinical variables that affect hs-cTn levels: age, sex, renal dysfunction, time from chest pain onset [4, 8, 12]

According to recent studies, the use of sex specific cut off levels was associated with an insignificant number of patients being reclassified in comparison with the use of a uniform cutoff level [27, 28]. Consequently, the use of sex-specific cutoff levels is not recommended by ESC so far [4]. Further studies are essential in order to determine the advantages or disadvantages of sex-specific cutoff levels in the diagnostic algorithms.

Patients with suspected MI and renal dysfunction are

in a higher risk of MI, than those with a normal kidney function [29]. The diagnosis of MI in these patients is very challenging, because in the first-place patients with renal dysfunction are more prone to an atypical clinical presentation of MI [30]. Moreover, they usually have left ventricular hypertrophy, which can mimic MI findings in ECG. Baseline cardiac troponin concentrations are also chronically elevated in renal dysfunction, in 10-20% of patients for cTn and in up to 70% of patients for hs-cTn, and are associated with poor prognosis [31]. The pathophysiology of high cTn levels is not fully understood, yet.

Even though baseline hs-cTn levels differ between patients with pathological and normal kidney function, there is no difference between them when it comes to measure absolute hs-cTn changes during serial sampling [32].

CONCLUSIONS

Hs-cTn tests combined with clinical evaluation and ECG findings, significantly contribute to the rapid management of patients with suspected MI. Although, these measurements are very useful for the early diagnosis of myocardial infarction, they may also be elevated in several other conditions associated with myocardial injury. Dynamic changes of hs-cTn levels during serial testing are helpful to differentiate ischemic from non-ischemic causes. The most important clinical advantage of hs-cTn assays is the fact that they can be used in the context of novel rapid strategies, allowing for early rule-in and rule-out of MI. Hs-cTn assays not only present a safe, and efficient way for the early detection and management of MI, but they also contribute to a significant reduction of costs and unnecessary investigations in the ED.

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Corresponding author:

Athanasios Moulias, MD, PhD, Consultant Cardiologist, Department of Cardiology, General University Hospital of Patras, Patras 26504, Greece; Tel.: +302613603281
E-mail: dramoulias@live.com

Diagnostic approach of fever due to zoonotic diseases in the rural population

Maria Lagadinou[1,2,3], Georgios Eleftherakis[1], Dimitris Papageorgiou[1], Themistoklis Paraskevas[1], Markos Marangos[1,2]

Abstract

Fever is frequent among people living in rural areas. Among others, zoonotic diseases are included in the differential diagnosis. Brucellosis is a disease of zoonotic origin affecting humans in several regions, with the highest impact in regions where productive animals constitute a significant income source. Leptospirosis is a zoonosis with global distribution and is considered as an emerging public health problem. Q fever is a worldwide zoonotic infection, caused by *Coxiella burnetii*. Leishmaniasis is a zoonosis and the parasite is transmitted by the bite of an infected female phlebotomine sand fly. West Nile is a zoonosis with multiple clinical manifestations. The aim of this review is to provide a general overview of the diagnostic approach of fever in people living in rural areas.

Key words: *Rural areas; leptospirosis; brucella; West Nile; Q fever; leishmaniasis*

INTRODUCTION

Febrile conditions are frequent among people living in rural areas. Among other illnesses, the most frequently diagnosed diseases in both rural and urban populations are zoonotic diseases.

Zoonotic diseases are diseases that can be transmitted naturally between vertebrate animals and humans. Such zoonoses can be transmitted either directly from animals to humans, or indirectly via food or the environment. Diseases that can be transmitted indirectly via the environment, such as leptospirosis and hantavirus disease, are particularly challenging to control as the natural environment also acts as a reservoir [1].

This article provides a general overview of the diagnostic approach of fever in people living in rural areas (Table 1). Adequate training of health workers is urgently needed since early diagnosis and proper treatment are critical.

[1]Department of Internal Medicine, University Hospital of Patras, Patras 26504, Greece
[2]Division of Infectious diseases, University Hospital of Patras, Patras 26504, Greece
[3]Department of Nursing, University of Patras, Patras 26334, Greece

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Brucellosis: Epidemiology, clinical symptoms and diagnosis

Brucellosis is a zoonotic disease affecting humans in several regions, with the highest impact in regions where productive animals constitute a significant income source. Among other countries of the Mediterranean basin, Greece is considered to be a country endemic for brucellosis with an enormous impact on livestock production, public health and, by extension, to the economy [2]. For the decade 2010-2019 the average annual incidence of cases in Greece was 1.02 cases per 100,000 population.

Brucella species are Gram-negative, small coccobacillus, intracellular bacteria that affect macrophages, dendritic cells, placental trophoblasts, and epithelial cells. *Brucella* species can survive under extreme conditions of temperature, humidity, pH, and survive in frozen and

Table 1. *Summary of all clinical manifestations and diagnostic tests for zoonotic diseases we have to consider in the differential diagnosis of fever in a patient living in a rural area.*

Type of Infection	Clinical Manifestation	Diagnostic Approach
Brucellosis	fever, headache, backache, weakness, weight loss, anorexia, mental depression	Rose Bengal test (RBT) PCR
Leptospirosis	Leptospiraemic phase (3-9 days): fever, chills, myalgia, headache. Conjunctival suffusion is a characteristic finding (3-4 days): severe myalgia, can usually involves the calf, abdomen (mimicking acute abdomen) and paraspinal muscles (resulting in meningism)	Microscopic agglutination test (MAT): 'gold standard' test Isolation of the organism from urine or tissues
Q fever	Flu-like illness: fever, sweats, cough (productive at times), myalgias, and arthralgias. A high percentage of patients also have pneumonia and hepatitis	Detection of phase I and II antibodies. A titer of 200 or greater for IgG and 50 or greater for IgM against phase II antibodies indicates a recent Q fever infection; an IgG titer of 800 or greater against phase I antibodies suggests chronic infection
Leismaniasis	Cutaneous disease presents as singular ulcerative or nodular lesions at or near the site of insect exposure	Microscopic observation and culture from adequate samples, Antigen detection, Serological tests, Detection of parasite DNA (PCR)
West Neil Fever	75-80% of infected persons may remain asymptomatic. 20-25% of infected patients typically experience the abrupt onset of fever, headache, fatigue and myalgias. Gastrointestinal complaints, including nausea and vomiting, have been frequently described. West Nile meningitis, is characterized by abrupt onset of fever and headache along with meningeal signs and photophobia	PCR IgM antibodies can be detected within 4 to 7 days after

aborted materials for longer durations [3].

In humans, brucellosis is caused by *B. melitensis, B. abortus* and *B. suis* which are transmitted by infected goats, pigs, sheep or cows to healthy humans. Exposure of humans to infected domestic animals or the consumption of milk or meat products derived from infected animals enhances the risk of acquiring brucellosis. The main source of *Brucella* infection in the urban population is usually contaminated food, milk or dairy products derived from infected animals. Farmers, farm laborers, animal attendants, shepherds, and veterinarians are at a higher risk of infection with *Brucella spp*. due to direct contact with infected animals or constant exposure to contaminated environments [3].

The main clinical symptoms of brucellosis in humans include intermittent fever, headache, backache, weakness, weight loss, anorexia and mental depression. Complications may occur in the gastrointestinal, cardiovascular, pulmonary, lymphatic, and nervous system. The involvement of the nervous system is termed neuro-brucellosis, and is characterized by fever, headache, psychosis, seizures, and behavioral changes [3,4].

The diagnosis of human brucellosis relies on three different modalities: culture, serology, and nucleic acid amplification tests (NAATs) [5]. The serological method, culture-based method, and molecular techniques are employed to detect *Brucella* infection in animals and humans. The detection of the microorganism in blood cultures makes it possible to confirm the presence of the disease in its early stages, when the serological tests results are still negative or show low or borderline antibody titers [5].

The routine method for the diagnosis of brucellosis includes the Wright test as the first screening test. The rose bengal test (RBT) is a card agglutination test that uses an 8% suspension of killed *B. abortus* strain

1119-3 cells stained with rose bengal dye and buffered to pH 3.65 ± 0.05. The RBT detects agglutinating and non-agglutinating antibodies and does not have the drawback of the prozone phenomenon [5]. PCR assay can be applied with serology for the diagnosis of brucellosis suspected cases and relapses regardless of the duration or type of the disease without relying on blood cultures, especially in chronic cases [4].

Leptospirosis: Epidemiology, clinical symptoms and diagnosis

Leptospirosis is a zoonotic disease with global distribution and is considered an emerging public health problem. Spirochaetes of the genus *Leptospira* account for the disease's clinical manifestations. All recognized species of *Leptospira* are categorized into 24 serogroups and 250 serovars based on the expression of surface-exposed lipopolysaccharide [6].

Leptospirosis is highly prevalent in the tropics, with 73% of cases occurring in this zone. It is common among rural farming populations and impoverished urban and semi-urban populations, particularly affecting young male adults. Farmers, those in contact with livestock, those exposed to rodents at their workplace, and people living in areas where sanitation is poor are at higher risk [7]. According to the Greek National Public Health Organisation (GNPHO), approximately 20 cases are reported annually and the incidence varies from 0.13 to 0.31 per 100,000 population depending on the geographical region of the country with seasonal variation [6].

Leptospirosis in humans can range from a mild, self-limiting acute febrile illness to a severe, life-threatening disease with multiple organs failure. Many organ systems can be involved, to varying degrees [7]. The initial 'leptospiraemic phase' lasts for three to nine days, and presents with non-specific symptoms: fever, chills, myalgia, and headache. Conjunctival suffusion is a characteristic finding, developing on the third to fourth day. Myalgia can be severe, and can usually involve the calf, abdomen (mimicking acute abdomen) and paraspinal muscles (resulting in meningism) [7].

The 'leptospiraemic' or 'septicaemic' phase is followed by an immune phase, where IgM antibodies appear in the blood, and organisms are excreted in the urine. A more severe form of the disease consists of conjunctival suffusion, jaundice, and acute kidney injury (Weil's syndrome). Pulmonary haemorrhage has recently been shown to be an important cause of mortality.

The 'gold standard' test currently available for the diagnosis is microscopic agglutination test (MAT), but it does not permit early diagnosis because it relies on detection of antibodies and cannot detect infection until 5–7 days after exposure [7]. Extremely helpful for the diagnosis are: a four-fold rise in MAT titers within a 2–3-week interval and also other assays such as PCR, culture, and immunofluorescent. Isolation of the organism from urine or tissues of the animals is the most reliable method to confirm infection due to *Leptospira* [6,7].

Q fever: Epidemiology, clinical symptoms and diagnosis

Q fever is a worldwide zoonotic infection, caused by *Coxiella burnetii*. Q fever infects a variety of hosts, including humans, ruminants (cattle, sheep, goats), pets, and, rarely, reptiles, birds, and ticks. Humans are exposed to the disease as other animals shed the organism in feces, urine, milk, and products of conception. These products contain large numbers of bacteria that become aerosolized after drying and remain virulent for months [8].

Acute Q fever has a wide spectrum of clinical manifestations. Clinical manifestations range from asymptomatic seroconversion, acute disease (ranging from a flu-like syndrome to severe pneumonia), or chronic disease (manifesting mainly as endocarditis or hepatitis) [9]. Most patients (50%-60%) who are infected with Q fever are asymptomatic. Acute Q fever is a self-limited disease in many cases, and even when clinical treatment is recommended, it resolves without adverse sequelae in most patients.

The most frequent presentation is a flu-like illness manifested by fever, sweats, cough (productive at times), myalgias, and arthralgias. A high percentage of patients also have pneumonia and hepatitis [8]. Endocarditis, the most common form of chronic Q fever (60%-70%), represents 3% to 5% of all endocarditis cases. Patients with both acute and chronic disease can have hepatosplenomegaly and hepatitis.

The diagnosis of Q fever relies mainly on serologic examination. Several laboratory studies are available, but antibody detection by immunofluorescence assay is the most commonly used method because of its high sensitivity and specificity. The most widely used serologic test is the detection of phase I and II antibodies. A titer of 200 or greater for IgG and 50 or greater for IgM against phase II antibodies indicates a recent Q fever infection; an IgG titer of 800 or greater against phase

I antibodies suggests chronic infection [8,9]. These cutoffs vary among laboratories and defined cutoffs for each individual test should be used [8]. Polymerase chain reaction, a promising test that may even be able to detect the presence of *C. burnetii* early in disease, is limited to reference laboratories and research studies.

Leismaniasis: Epidemiology, clinical symptoms and diagnosis

Leismaniasis is a vector-borne infectious disease, caused by the genus *Leishmania*. It is a zoonosis and the parasite is transmitted by the bite of an infected female phlebotomine sand fly. It is among the deadliest neglected tropical diseases, afflicting nearly 700,000 to 1 million people annually [10]. The disease is endemic in tropical and subtropical regions.

Clinically, it is subdivided into visceral (kala-azar), cutaneous and mucocutaneous forms. Visceral leishmaniasis (VL), the most severe form, is a disseminated intracellular protozoan infection that targets tissue macrophages in the liver, spleen and bone marrow [11]. Leishmanial disease causes three main human syndromes: 1. cutaneous disease presents as singular ulcerative or nodular lesions at or near the site of insect exposure. These are usually found on uncovered areas of the body such as the face, forearms and lower legs and evolve over weeks to months, 2. Mucocutaneous disease, an infection resulting from the chronic local destruction of tissue of the nose, mouth oro- and nasopharynx and eyelids. It can progress to affect respiratory function and hamper nutrition 3. Visceral leishmaniasis (VL) results from the infection of phagocytes within the reticuloendothelial system due to the metastasis of parasites and parasite-infected macrophages from the initial site of cutaneous infection [12].

Leishmania infantum can both cause VL, but *L. infantum* is the predominant pathogen in Mediterranean countries. Laboratory diagnosis of VL includes microscopic observation and culture from adequate samples, antigen detection, serological tests, and detection of parasite DNA [13]. Definitive diagnosis is supported by direct demonstration of parasites in clinical specimens and specific molecular methods. PCR protocols to detect *Leishmania* DNA in VL diagnosis have used a variety of samples, including spleen, lymph node, and bone marrow aspirates, whole blood, and buffy coat [13].

The culture of the parasite can improve diagnostic sensitivity, but is time- consuming, and expensive, and thus seldom used for clinical diagnosis. ELISA is the preferred laboratory test for serodiagnosis of VL. This technique is highly sensitive, but its specificity depends upon the antigen used. Moreover, this assay can be performed easily [13].

West Neil Fever: Epidemiology, clinical symptoms and diagnosis

West Nile virus (WNV) is 1 of more than 70 viruses of the family *Flaviviridae* of the genus *Flavivirus*. Serologically, West Nile virus is a member of the Japanese encephalitis serocomplex, which includes Japanese encephalitis virus and an endemic North American flavivirus, St Louis encephalitis virus [14]. Mosquito bites are responsible for nearly all human infections. West Nile virus can also be transmitted via transfused platelets, red blood cells, and fresh frozen plasma as well as through heart, liver, lung, and kidney transplants. Transmission via organ transplant has occurred from donors without detectable viremia, suggesting viral sequestration in organs shortly after viremia has cleared [14].

The incubation period for clinical symptoms ranges from 2 to 14 days, but prolonged incubation periods of up to 21 days have been observed among immunocompromised patients. Following the incubation, 75-80% of infected persons may remain asymptomatic. About 20-25% of infected patients typically experience the abrupt onset of fever, headache, fatigue and myalgias. Gastrointestinal complaints, including nausea and vomiting, have been frequently described [15]. West Nile meningitis, is characterized by the abrupt onset of fever and headache along with meningeal signs and photophobia. West Nile Encephalits (WNE) may range in severity from a mild, self-limited confusional condition to severe encephalopathy, coma and death. This manifestation is more commonly seen in older individuals, particularly over the age of 55, as well as immunocompromised persons [14].

Because the virus is present at very low levels in human blood and tissues, real-time PCR-based detection systems are recommended for the rapid detection of WNV infection in clinical samples [16]. Following exposure to WNV, both IgM and IgG antibodies are produced. In most cases, IgM antibodies can be detected within 4 to 7 days after the initial exposure and may persist for more than one year. In contrast, anti-WNV IgG are reliably detected approximately 8 days after the onset of symptoms and they have a limited use in the initial diagnosis of WNV infection [16].

The management of patients with WNV encephalitis

or encephalomyelitis is a challenging problem since there is currently no definitive treatment for WNV infection. The prevention of infection through protection from mosquito bites is therefore critical and the single most important public health measure. The management of illness due to WNV infection remains supportive. Patients with otherwise uncomplicated WNV infection generally do not require specific intervention. Patients with severe WN infection require symptomatic therapy such as pain control for severe headache.

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Corresponding author:

Maria Lagadinou, Assistant Professor of Internal Medicine,
Department of Nursing, University of Patras, Greece
& Department of Internal Medicine,
University Hospital of Patras, Greece
E-mail: m_lagad2004@yahoo.gr

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