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European practice patterns for antiplatelet management in NSTE-ACS patients: Results from the REal-world ADoption survey focus on Acute antiPlatelet Treatment (READAPT) survey

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ABSTRACT

Background: The 2020 European Society of Cardiology (ESC) guidelines for the diagnosis and management of patients with non-ST elevation-acute coronary syndrome (NSTE-ACS) recommend early invasive coronary angiography in high-risk patients and no routine pre-treatment with oral P2Y12 receptor inhibitor in NSTE-ACS patients prior to defining coronary anatomy.
Objective: To assess the implementation of this recommendation in the real-life setting.
Methods: A web-survey in 17 European countries collected physician profiles and their perceptions of the diagnosis, medical and invasive management of NSTE-ACS patients at their hospital. A sample size of at least 1100 responders permitted the estimation of proportions with a precision of at least ±3.0%.
Results: Among the 3024 targeted participants, 1154 provided valid feedback defined as a 50% response rate of answers to the survey questions. Overall, >60% of the participants declared full implementation of the guidelines at their institution. The time delay from admission to coronary angiography and PCI was reported to be <24 h in over 75% of the hospitals while pre-treatment was intended in >50% of NSTE-ACS patients. Ad-hoc percutaneous coronary intervention (PCI) was performed in >70% of the cases while intravenous platelet inhibition was rarely used (<10%). Between countries differences in practice patterns for antiplatelet management for NSTE-ACS were observed, suggesting heterogeneous implementation of the guidelines.
Conclusions: This survey indicates that the implementation of 2020 NSTE-ACS guidelines on early invasive management and pre-treatment is heterogeneous, potentially due by local logistical constraints.

1. Introduction

Platelet inhibition is essential in the management of patients with suspected non-ST elevation-acute coronary syndrome (NSTE-ACS) [1], particularly in those undergoing percutaneous coronary intervention (PCI) [2]. While the use of aspirin as a first line antiplatelet agent remains undisputed, oral P2Y12 receptor inhibitor initiation before the coronary anatomy is known, defined as pre-treatment, remains a matter of debate [3–5]. The updated 2020 European Society of Cardiology (ESC) guidelines for the diagnosis and management of patients with NSTE-ACS recommend to postpone their administration until the coronary anatomy has been defined, particularly when an early invasive

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management is planned [6].

While the early use of oral P2Y12 receptor inhibition was advocated in the era when the time to an invasive evaluation was delayed by several days [7], contemporary studies with shorter time delays and more potent drugs have failed to show additional benefit in this strategy and identified a consistent increased risk of bleeding [8–13]. The relevance of a tailored and more individualized approach to antiplatelet therapy to reduce bleeding complications, and the potential benefit of a rapid invasive coronary strategy for higher-risk patients have been articulated in clinical guidelines [6]. In particular, an updated guidance on the use of intravenous antiplatelet therapies for patients undergoing PCI has also been provided [6].

Adherence to the 2020 ESC guidelines on NSTE-ACS patients was recently analysed in a national survey in Germany's certified chest pain units (CPUs) [14]. Moreover, an international crowdsourcing survey on the treatment of NSTE-ACS high bleeding risk patients undergoing PCI [15] demonstrated a high variability on dual antiplatelet therapy (DAPT) duration, the choice of monotherapy and risk stratification. European practices and standards of antiplatelet therapies in the management of NSTE-ACS patients and their alignment with the 2020 ESC guidelines have yet to be unexplored. We undertook a survey to assess clinical practices patterns on timing of angiography and use of antiplatelet therapies in the management of NSTE-ACS patients in Europe. Our primary aim was to gather insights about guideline implementation and potential barriers.

2. Participants and methods

2.1. Design

A web-based questionnaire was developed according to the most relevant literature reviews and was validated by a scientific committee (SC) comprised of four cardiologists (JP·C, G.M, C.P.G, D.A) from different geographic regions with extensive expertise in the treatment of ACS patients.

Physician profile and hospital characteristics were collected and a specific section on diagnosis, and medical and invasive management of NSTE-ACS patients was developed. The questionnaire was hosted on an online dedicated platform available between 4 February 2022 and 15 April 2022. All the services were accessible via the Internet on a secure internet connection (HTTPS) using a valid TLS certificate (bidirectional encrypted communication). The questionnaire can be found in the Supplement section.

2.2. Participants

Physicians were invited via email from the available distribution listings extracted from Chiesi Farmaceutici S.p.A, and its affiliates or from external providers proprietary databases for each country involved. Extended scouting was performed to collect a contact database covering all the target countries. The physicians contacted had to read and acknowledge a legal release message to be able to access the questionnaire. The participant inclusion criteria applied to interventional cardiologists and non-invasive hospital-based cardiologists who managed patients with NSTE-ACS and agreed to participate in the research. The following countries were included: Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Norway, Slovenia, Spain, Sweden, Switzerland, the Netherlands, Turkey and the United Kingdom. Due to their small sample size, Denmark, Finland, Norway and Sweden were analysed jointly (Nordic countries). Participants who did not meet the aforementioned criteria were not invited to participate.

2.3. Sample size

A target precision of around ±3% (i.e., a 95% confidence interval width of 6%) was established for this study. A sample size of at least 1100 responders permitted the estimation of proportion with a precision of at least ±3.0%. Based on the 3024 target cardiologists contacted, a valid sample of 1154 responders was achieved. Responders (valid sample) were defined as participants who documented the country where they worked and their specialty in the declarative part of the questionnaire and who completed at least 50% of the questions about acute antiplatelet management. This sample size permitted an overall precision of 2.74% and by-country precision.

2.4. Statistical analysis

All variables were categorical and described as numbers and percentages. Percentages were calculated from the numbers of observed data. Proportions between variables or independent groups were compared using the Chi-squared test and a p-value <0.05 was considered statistically significant. Descriptive statistics referred to the overall sample were calculated using the calculated weights to correct the actual sample achieved according to the theoretical sample distribution by country. Weights were based on the known distribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Atlas [16]. For Austria and the Czech Republic the EAPCI Atlas distribution is not known, hence the data from these countries were combined with those of known distribution. A by-country descriptive analysis was also provided, in which case no weighting was applied. Metrics were also evaluated according to the number of PCIs performed by year (<300, 300–700, 700–1000, 1000–1300, >1300). Analyses were conducted using SPSS Statistics 26.

3. Results

3.1. Study population

The study sample consisted of 1154 interventional cardiologists and non-invasive hospital-based cardiologists from 17 European countries who participated in the READAPT survey (Fig. 1A). The overall sample consisted of a similar number of interventional cardiologists (53.90%) and non-invasive hospital-based cardiologists (46.10%). However, some countries such as Austria, the Czech Republic, Italy and Turkey had a significantly higher proportion of interventional cardiologists compared to hospital cardiologists (Fig. 1B).

3.2. Time to invasive procedure

In most hospitals (76.5%), NSTEMI patients receive invasive coronary angiography within 24 h after admission, with significant heterogeneity between countries ($p < 0.0001$). For example, invasive coronary angiography was reported to be performed in <24 h in over 95% of the hospitals in the Czech Republic, Germany and Turkey, whereas this goal was achieved in fewer than 30% of the hospitals in the UK (Fig. 2A). PCI was performed immediately or within 2 h after invasive coronary angiography in 71.3% and in 9.7% of the hospitals, respectively. Differences in time to PCI following invasive coronary angiography was also reported between countries ($p < 0.0001$) with >90% in Italy (94%) having immediate PCI versus 60% in France, Greece and the Netherlands. In the UK and the Netherlands, the time to PCI was reported to be >24 h in 15.9% and in 13.8% of the hospitals, respectively (Fig. 2B).

Significant differences in time to PCI were observed between centres according to the number of PCIs performed by year (<300, 300–700, 700–1000, 1000–1300, >1300) ($p = 0.002$), with more time to PCI (>24 h) in centres with lower volume (<300 PCIs). Data was homogeneous between countries (data not shown). Differences in time to PCI following invasive coronary angiography was also reported between PCIs performed by year, with fewer PCIs performed immediately after angiography in centres performing <300 PCIs per year (data not

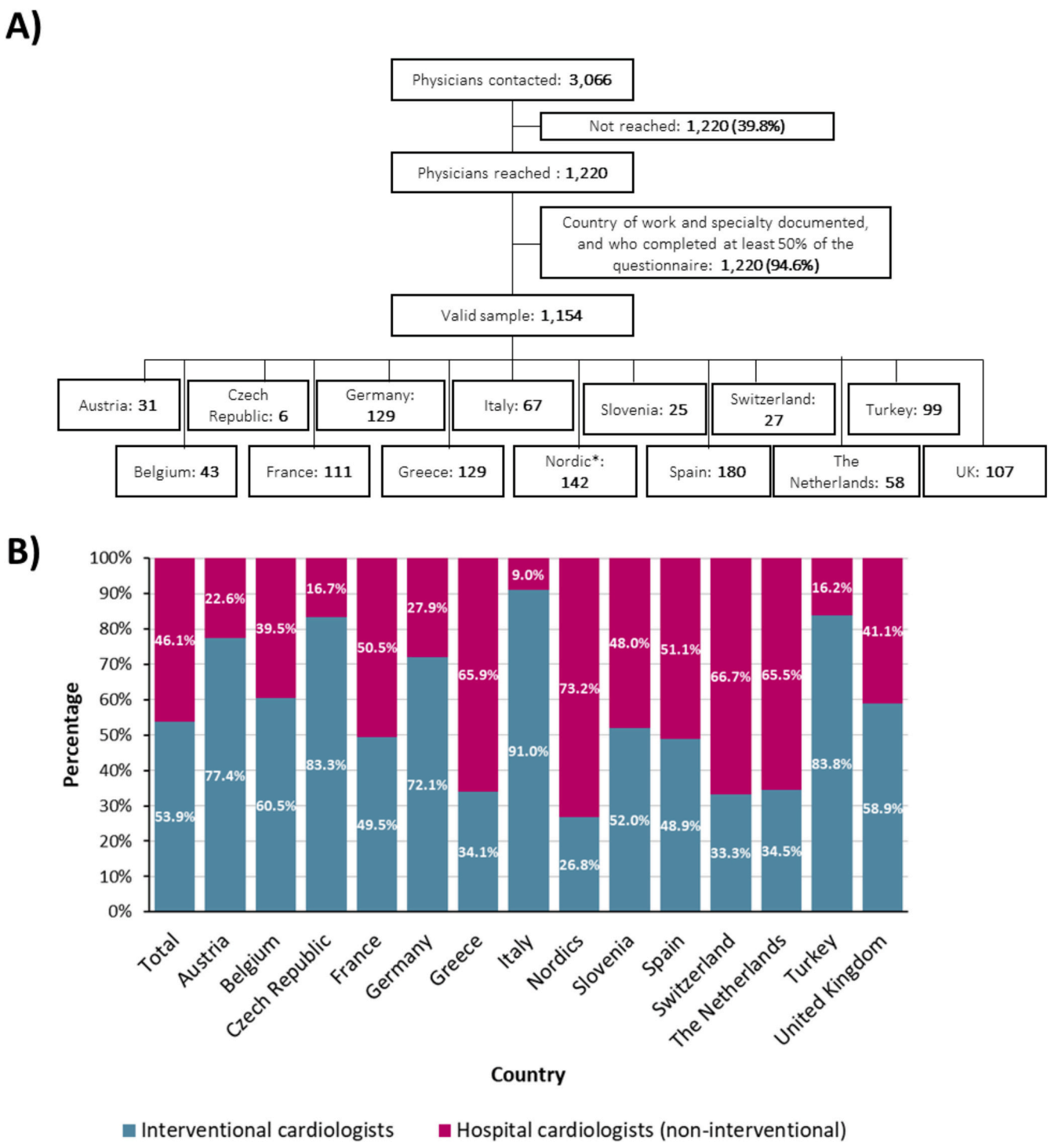

Fig. 1. Study population. A) Valid sample flow chart. B) Participants' specialty: overall and by country. *Nordic: Denmark, Finland, Norway, Sweden.

shown).

3.3. Pre-treatment with oral P2Y12 inhibitors

Overall, half of patients with suspected NSTE-ACS (NSTEMI and unstable angina) are declared to be pre-treated with an oral P2Y12 receptor inhibitor (55.3%). In Italy, this proportion was <25% in the majority of hospitals (59.7%) while in the UK, all patients were reported to be pre-treated with an oral P2Y12 receptor inhibitor in 35.5% of the hospitals (Fig. 3A). Pre-treatment was mostly initiated (69.7%) in the emergency room, followed by in the intensive care unit (ICU) prior to the catheterisation lab (Fig. 3B). Respondents stated that a decision to pre-treat was mainly based upon bleeding risk, NSTE-ACS type (unstable angina vs NSTEMI) and ischaemic risk. This pattern was similar in most other surveyed countries, although in the Czech Republic and Slovenia, almost 80% of the use of oral P2Y12 receptor inhibition was reported to be based upon ischaemic risk alone (Fig. 3C). When considering the percentage of patients receiving pre-treatment with oral P2Y12 inhibitors according to the number of PCIs performed by year (<300, 300–700, 700–1000, 1000–1300, >1300), no significant differences between categories were found overall or by country (data not shown). Pre-treatment was mostly initiated in the emergency room, although

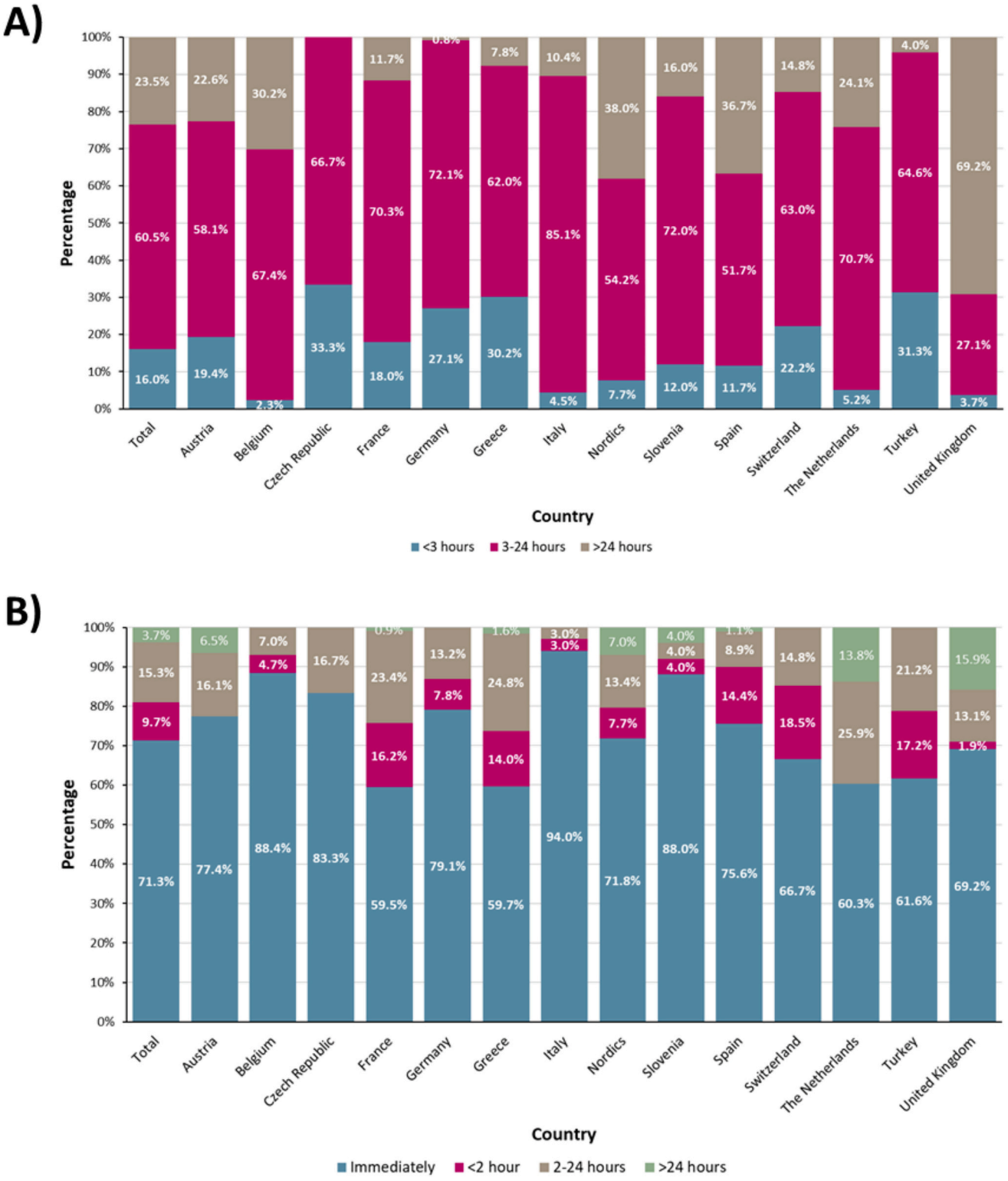

Fig. 2. Time to invasive procedures: overall and by country. A) Time from admission to coronary angiography. B) Time from coronary angiography to percutaneous coronary intervention.

low-PCI-volume centres showed less initiation during ambulance transport to the hospital and immediately before coronary angiography than high-PCI-volume hospitals, with significant differences overall (data not shown). Similarly, the decision to pre-treat was significantly lower in low-PCI-volume centres (data not shown).

Among non-pre-treated NSTEMI patients, ticagrelor (60.2%) was the most commonly used oral P2Y12 receptor inhibitor, followed by clopidogrel (22.6%) and prasugrel (15.5%). The comparison between countries ($p < 0.0001$) found that ticagrelor was the most frequently prescribed oral P2Y12 receptor inhibitor among participating countries except Greece, where clopidogrel is used the most in 50% of the hospitals (Fig. 3D).

No significant differences in the oral P2Y12 receptor inhibitor between centres according to the number of PCIs performed by year were

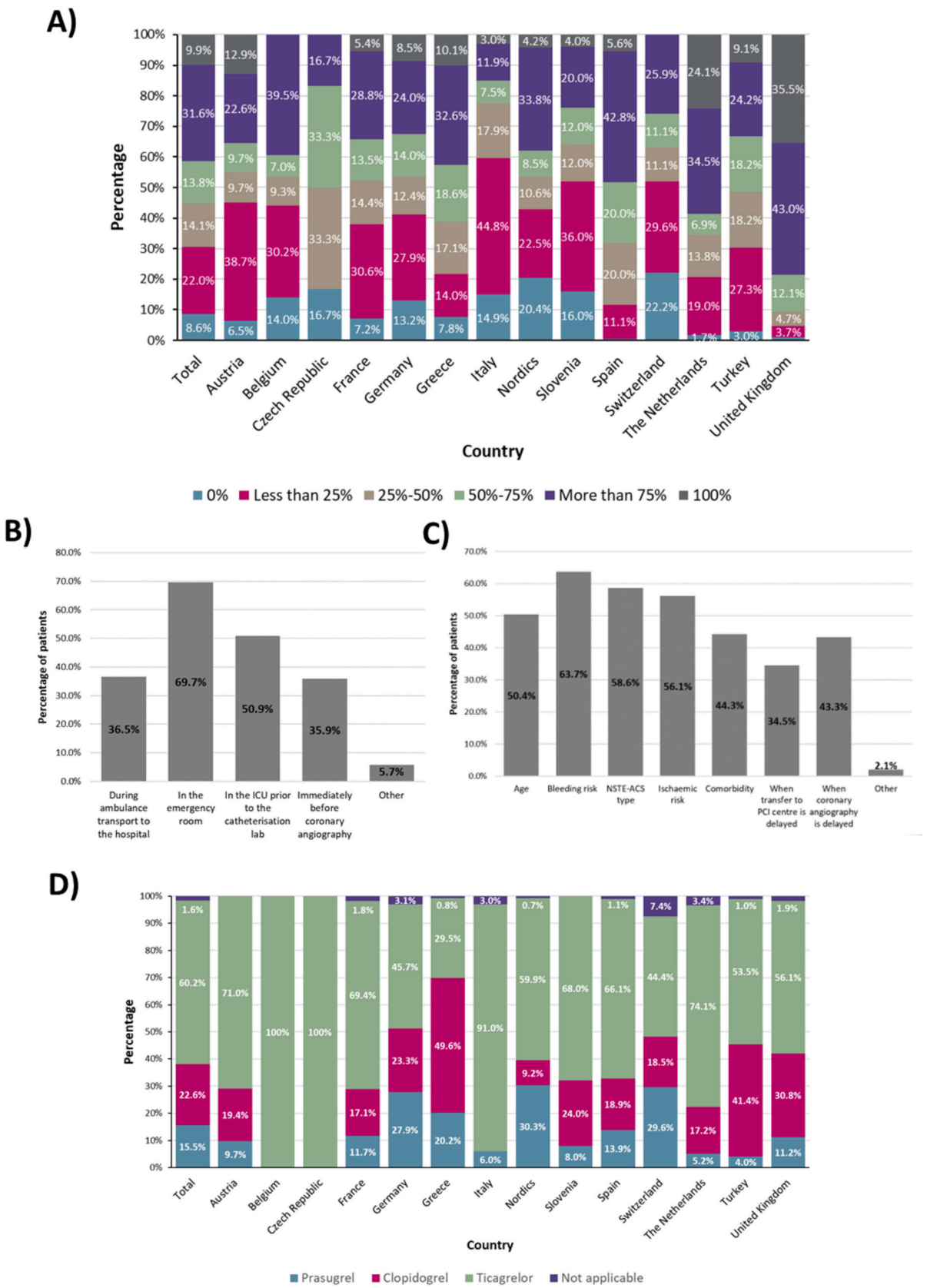

Fig. 3. European clinical scenario for pre-treatment in NSTE-ACS patients. A) Proportion of NSTE-ACS patients pre-treated with oral P2Y12 receptor inhibitors overall and by country. B) Sites of initiation of oral P2Y12 receptor inhibitor pre-treatment, overall. C) Reasons for oral P2Y12 receptor inhibitor pre-treatment, overall. D) Different oral P2Y12 receptor inhibitors in non-pre-treated NSTEMI patients: overall and by country.

observed overall (data not shown). However, significant differences in the oral P2Y12 receptor inhibitor used according to the number of PCIs performed by year (<300, 300–700, 700–1000, 1000–1300, >1300) were observed in Italy ($p < 0.0001$), Spain and The Netherlands ($p = 0.016$, for both) (data not shown). In Italy ticagrelor was the most frequently in low-PCI-volume centres. In Spain, ticagrelor was the most frequently prescribed P2Y12 receptor inhibitor, with higher use in centres performing a higher number of PCIs by year (>1300). In contrast, clopidogrel was more used in centres performing a lower number of PCIs by year (30% in centres with <300 PCIs by year vs. 14.8% in centres with >1300 PCIs per year). In centres performing 700–1000 PCIs by year, the use of prasugrel reached 27.3%, vs. ~10% in centres performing high (>1300) or low number of PCIs by year (⟨300). In The Netherlands, ticagrelor was the most frequently prescribed P2Y12 receptor inhibitor in centres performing high (>1300) or low number of PCIs by year (<300), while clopidogrel was the P2Y12 receptor inhibitor most used in centres performing 700–1000 PCIs by year (data not shown).

Furthermore, respondents stated that the ESC clinical practice guideline recommendation "it is not recommended to administer routine pre-treatment with a P2Y12 receptor inhibitor to patients in whom the coronary anatomy is not known and early invasive management is planned" had been implemented in 63% of the hospitals in which they practice (Supplementary Fig. S1A). No significant differences were observed between centres according to the number of PCIs performed by year (data not shown).

3.4. Intravenous antiplatelet treatments

In most hospitals (68.8%), intravenous P2Y12 receptor inhibitors (i.e., cangrelor) were reported to be used in <10% of NSTEMI patients who were not pre-treated with an oral P2Y12 inhibitor (Fig. 4A). Similarly, GP IIb/IIIa antagonists were used in <10% of NSTEMI patients who were not pre-treated with an oral P2Y12 inhibitor in 66.8% of the hospitals (Fig. 4B). Accordingly, 85.9% of the participants stated that their centres had implemented the recommendations of 2020 ESC guidelines for NSTE-ACS patients to consider GP IIb/IIIa antagonists for bail-out situations only (Supplementary Fig. S1B). When considering these according to the PCIs performed per year, no significant differences were found in any cases (data not shown).

4. Discussion

The present European survey found that: a) in most countries, the time delay from admission to invasive coronary angiography and PCI is in accordance with the 2020 ESC guidelines; b) there is heterogeneity in the proportion of NSTE-ACS patients who are pre-treated with an oral P2Y12 receptor inhibitor, which is mainly initiated in the emergency room; and c) ticagrelor is the most commonly used oral P2Y12 receptor inhibitor in non-pre-treated patients, while intravenous P2Y12 receptor inhibitors and GP IIb/IIIa antagonists are used in <10% of patients who are not pre-treated.

Based on the TIMACS [17] and the VERDICT [18] randomized controlled trials, the 2020 ESC guidelines [6] recommend an early invasive strategy (<24 h from hospital admission) in high-risk patients defined as the presence of one of the following: established NSTEMI diagnosis; dynamic new or presumably new contiguous ST/T-segment changes (symptomatic or silent); resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock; GRACE risk score > 140. These high-risk criteria are derived from pre-defined subgroup analyses of the above-cited studies and one patient-level data meta-analysis [19]. The early invasive approach to the management of NSTE-ACS is frequently challenged given that reduction in refractory angina is the only identified clinical benefit, without benefits in strong endpoints (mortality) neither conclusive evidence for improvement of cardiac biomarkers [20]. More recent analyses from large registries [21] suggest that symptom onset-to-catheterization >48 h may better predict outcome rather admission to catheterization time delay. Considering such approach would allow more flexibility particularly for centres without on-site catheterization lab services. Indeed, previous studies show that delayed invasive coronary strategies are mostly due to logistical and patients constraints (such as a limited number or lack of catheterisation labs, high number of patients, limited staff, and pre-hospital delays) [22–26]. Furthermore, delays to invasive coronary angiography seem to occur mostly in countries with higher rates of pre-treatment, suggesting a correlation between time to invasive strategies and oral P2Y12 receptor inhibitor pre-treatment.

A high proportion of NSTE-ACS patients were pre-treated in most of the hospitals of the participating countries. Uncertainty of evidence and logistical reasons likely account for these discrepancies between evidence-based and clinical practice [22–25,27]. Pre-treatment may be considered in high-risk patients at low bleeding risk who are not eligible for an early invasive angiography. In the CURE PCI study [17], pre-treatment with clopidogrel led to a potential benefit in patients with prolonged delays to invasive coronary angiography. Yet, pre-treatment with oral P2Y12 inhibitors (either clopidogrel, prasugrel and ticagrelor) has been found to be associated with increased bleeding risk in patients who require coronary artery bypass graft surgery, among those with an alternate diagnosis [28–30] as well as in those pre-treated with prasugrel receiving PCI [31].

The 2020 ESC guidelines recommend considering prasugrel over ticagrelor for NSTE-ACS patients who are scheduled for PCI and that clopidogrel be used only when prasugrel or ticagrelor are not available, cannot be tolerated or are contraindicated [6,32]. Our survey indicates that these recommendations are not reported to be followed by most hospitals. The class III recommendation for the use of prasugrel before coronary anatomy is known and may explain such finding, since pre-treatment is perceived to occur broadly with ticagrelor, the preferred agent.

Cangrelor, the only available intravenous P2Y12 receptor inhibitor, is used in <10% of the participating hospitals, although it may be considered as an option in P2Y12 receptor inhibitor-naïve NSTE-ACS patients undergoing PCI [6]. The fact that the comparator arm in the trials testing the efficacy of cangrelor was clopidogrel [33,34], while prasugrel and ticagrelor – known to have superior efficacy over clopidogrel in NSTE-ACS patients and accordingly also recommended over clopidogrel in the ESC guidelines – were never tested against cangrelor may account for such a finding. More studies are needed to test the potential benefits of cangrelor over newer generation oral P2Y12 receptor inhibitors that thus far are limited to pharmacodynamic investigations [35–37].

Most trials analysing the value of GP IIb/IIIa antagonists were conducted before the era of routine DAPT [38]. Nowadays, however, although GP IIb/IIIa antagonists have potent platelet inhibitory effects, they present a higher risk of bleeding and may therefore only be considered for bail-out situations if there is evidence of no-reflow or a thrombotic complication [6]. Our survey identified that most hospitals appear to follow the 2020 ESC guideline recommendations on the use of GP IIb/IIIa antagonists.

We recognise that our survey has limitations. Firstly, it was based on a questionnaire that compiled participants' perspectives. As such, the results should be interpreted with caution and as perceptions of the respondents. Secondly, measures were not taken to ensure that all the realities in a country were well represented, meaning that some geographical areas in a country might not be represented and bias cannot be excluded. Thirdly, the response rate of invited participant was <70% of the target number of potential candidates, which may result selective non-response effects. Forth, the small sample size of some countries meant that they had to be analysed jointly and the reality in those specific countries could not be well determined. Five, no information was collected regarding whether respondents worked or not in a hospital with a catheterisation lab with 24/7 capability. Onsite

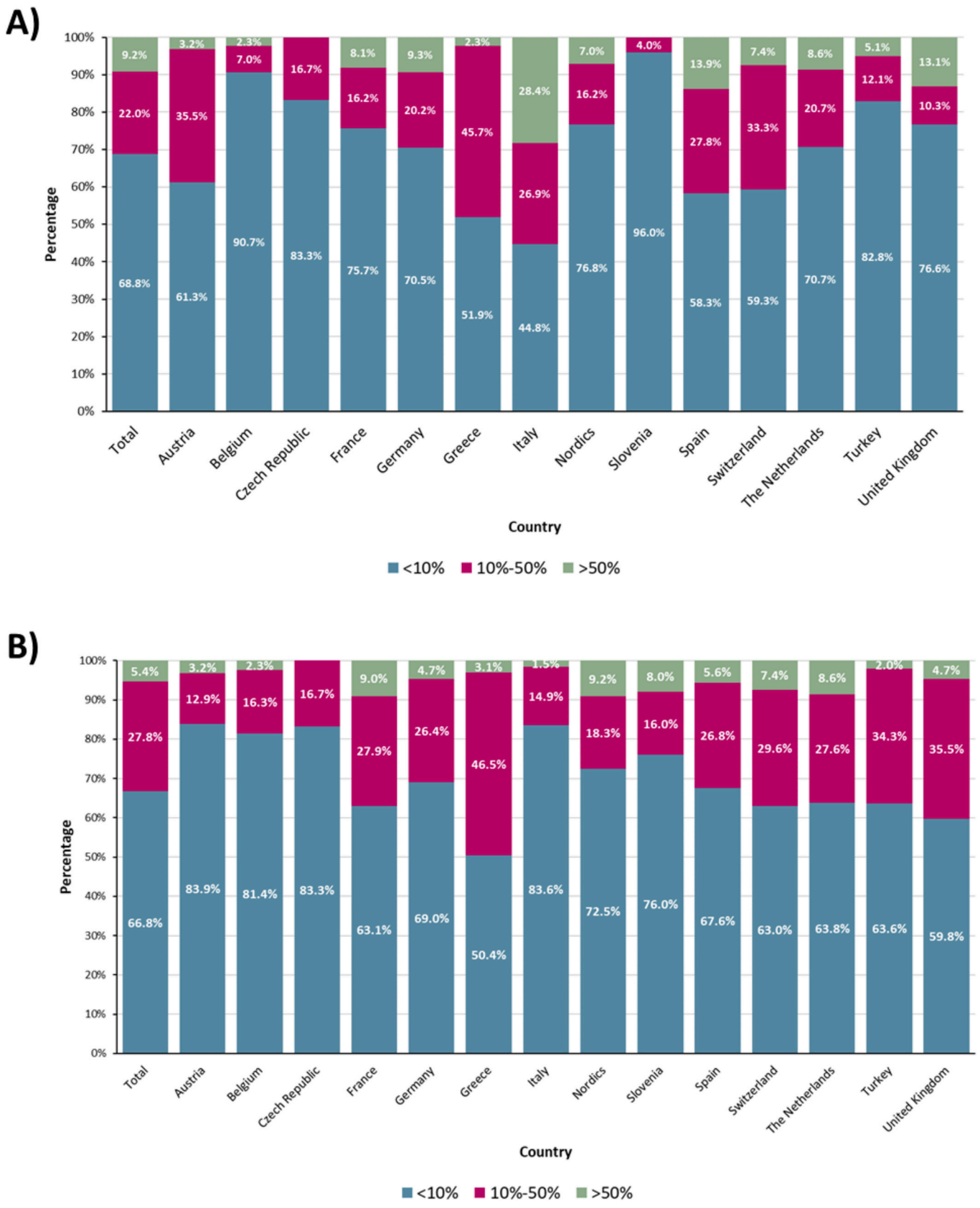

Fig. 4. European usage of intravenous antiplatelet treatments. A) Rate of intravenous P2Y12 receptor inhibitor used in NSTEMI patients not pre-treated with oral P2Y12 inhibitor: overall and by country. B) Percentage of intravenous GP IIb/IIIa antagonists used in NSTEMI patients who are not pre-treated with oral P2Y12 inhibitor: overall and by country.

availability of PCI may have influenced the decision to pre-treat, and therefore, biased the survey results. Finally, the survey did not ask whether the center was academic or not, thus data on antiplatelet approaches according to the type of hospital was not available.

5. Conclusions

The READAPT Project reflects the participants' perception that early invasive coronary angiography is the predominant approach to the management of high-risk NSTE-ACS patients, and that routine pre-treatment with oral P2Y12 inhibitor remains high despite not being guideline recommended. Geographic variation in the use of oral P2Y12 inhibitor pre-treatment was observed, suggesting heterogeneous implementation of the guidelines. Local-level logistical constraints as well as a more nuanced definition of what constitutes a high-risk patient with NSTEMI may be barriers to optimal implementation of guideline recommended care.

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Declaration of Competing Interest

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